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SUBSTITUTED BENZAZOLES AND USE THEREOF AS INHIBITORS OF RAF KINASE ;

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ABSTRACT:

New substituted benzazole compounds of formula (I), compositions and methods of inhibition of Raf kinase activity in a human or animal subject are provided. The new compounds compositions may be used either alone or in combination with at least one additional agent for the treatment of a Raf kinase mediated disorder, such as cancer.

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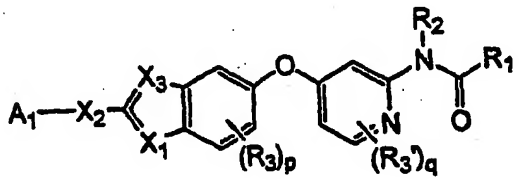
(54) Title: SUBSTITUTED BENZAZOLES AND USE THEREOF AS INHIBITORS OF RAF KINASE



(I)

(57) Abstract: New substituted benzazole compounds of formula (I), compositions and methods of inhibition of Raf kinase activity in a human or animal subject are provided. The new compounds compositions may be used either alone or in combination with at least one additional agent for the treatment of a Raf kinase mediated disorder, such as cancer.

SUBSTITUTED BENZAZOLES AND USE THEREOF AS INHIBITORS OF RAF KINASE

FIELD OF THE INVENTION

The present invention relates to new substituted benzazole compounds and pharmaceutically acceptable salts, esters or prodrugs thereof, compositions of the new compounds together with pharmaceutically acceptable carriers, and uses of the new compounds, either alone or in combination with at least one additional therapeutic agent, in the prophylaxis or treatment of cancer.

BACKGROUND OF THE INVENTION

The Raf serine/threonine kinases are essential components of the Ras/Mitogen-Activated Protein Kinase (MAPK) signaling module that controls a complex transcriptional program in response to external cellular stimuli. Raf genes code for highly conserved serine-threonine-specific protein kinases which are known to bind to the ras oncogene. They are part of a signal transduction pathway believed to consist of receptor tyrosine kinases, p21 ras, Raf protein kinases, Mek1 (ERK activator or MAPKK) kinases and ERK (MAPK) kinases, which ultimately phosphorylate transcription factors. In this pathway Raf kinases are activated by Ras and phosphorylate and activate two isoforms of Mitogen-Activated Protein Kinase Kinase (called Mek1 and Mek2), that are dual specificity threonine/tyrosine kinases. Both Mek isoforms activate Mitogen Activated Kinases 1 and 2 (MAPK, also called Extracellular Ligand Regulated Kinase 1 and 2 or Erk1 and Erk2). The MAPKs phosphorylate many substrates including transcription factors and in so doing set up their transcriptional program. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular functions such as proliferation, differentiation, survival, oncogenic transformation and apoptosis.

Both the essential role and the position of Raf in many signaling pathways have been demonstrated from studies using deregulated and dominant inhibitory Raf mutants in mammalian cells as well as from studies employing biochemical and genetic techniques model organisms. In many cases, the activation of Raf by receptors that stimulate cellular tyrosine phosphorylation is dependent on the activity of Ras, indicating that Ras functions upstream of Raf. Upon activation, Raf-1 then phosphorylates and activates Mek1, resulting in the propagation of the signal to downstream effectors, such as MAPK (mitogen-activated protein kinase) (Crews et al. (1993) *Cell* 74:215). The Raf

serine/threonine kinases are considered to be the primary Ras effectors involved in the proliferation of animal cells (Avruch et al. (1994) *Trends Biochem. Sci.* 19:279).

Raf kinase has three distinct isoforms, Raf-1 (c-Raf), A-Raf, and B-Raf, distinguished by their ability to interact with Ras, to activate MAPK kinase pathway, tissue distribution and sub-cellular localization (Marias et. al., *Biochem. J.* **351**: 289-305, 2000; Weber et al., *Oncogene* **19**:169-176, 2000; Pritchard et al., *Mol. Cell. Biol.* 15:6430-6442, 1995). Raf kinases are activated by Ras and phosphorylate and activate two isoforms of Mitogen-Activated Protein Kinase Kinase (called Mek1 and Mek2) that are dual specificity threonine/tyrosine kinases. Both Mek isoforms activate Mitogen Activated Kinases 1 and 2 (MAPK, also called Extracellular Ligand Regulated Kinase 1 and 2 or Erk1 and Erk2). The MAPKs phosphorylate many substrates including cytosolic proteins and ETS family of transcription factors. Raf kinase participation in the Ras/MAPK pathway influences and regulates many cellular functions such as proliferation, differentiation, survival, cell cycle progression and apoptosis.

Activating mutation of one of the Ras genes can be seen in ~20% of all tumors and the Raf/MEK/ERK pathway is activated in ~30% of all tumors (Bos et. al., *Cancer Res.* **49**:4682-4689, 1989) (Hoshino et. al., *Oncogene* **18**:813-822, 1999). Recent studies have shown that B-Raf mutation in the skin nevi is a critical step in the initiation of melanocytic neoplasia (Pollock et. al., *Nature Genetics* **25**:1-2, 2002). Furthermore, most recent studies have emerged that activating mutation in the kinase domain of B-Raf occurs in ~66% of melanomas, 12% of colon carcinoma and 14% of liver cancer (Davies et. al., *Nature* **417**:949-954, 2002) (Yuen et. al., *Cancer Research* **62**:6451-6455, 2002) (Brose et. al., *Cancer Research* **62**:6997-7000, 2002).

Inhibitors of Raf/MEK/ERK pathway at the level of Raf kinases can potentially be effective as therapeutic agents against tumors with over-expressed or mutated receptor tyrosine kinases, activated intracellular tyrosine kinases, tumors with aberrantly expressed Grb2 (an adapter protein that allows stimulation of Ras by the Sos exchange factor) as well as tumors harboring activating mutations of Raf itself. In the early clinical trails inhibitor of Raf-1 kinase that also inhibit B-Raf have shown promise as therapeutic agents in cancer therapy (Crump, *Current Pharmaceutical Design* **8**: 2243-2248, 2002; Sebastien et. al., *Current Pharmaceutical Design* **8**: 2249-2253, 2002). In addition, an orally administered Raf kinase inhibitor that inhibits both B-Raf and C-Raf, BAY 43-9006, is currently undergoing worldwide clinical evaluation in phase I and II

clinical studies in patients with a variety of malignancies, including melanomas (Tuveson et al., *Cancer Cell* **4:** 95-98, 2003).

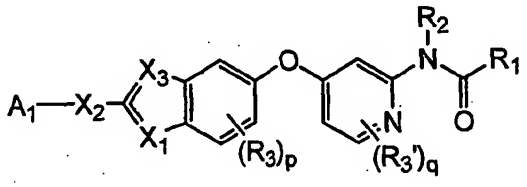
Disruption of Raf expression in cell lines through the application of RNA antisense technology has been shown to suppress both Ras and Raf-mediated tumorigenicity (Kolch et al., *Nature* **349:**416-428, 1991; Monia et al., *Nature Medicine* **2(6):**668-675, 1996). In recent studies, reduction in B-Raf levels with RNA interference in melanoma cells resulted in a profound inhibition of the MAP kinase cascade, diminished proliferative capacity, and the inability to support anchorage-independent cell growth (Tuveson et al., *Cancer Cell* **4:** 95-98, 2003).

Several Raf kinase inhibitors have been described as exhibiting efficacy in inhibiting tumor cell proliferation in *vitro* and/or *in vivo* assays (see, *e.g.*, U.S. Pat. Nos. 6,391,636, 6,358,932, 6,037,136, 5,717,100, 6,458,813, 6,204,467, and 6,268,391). Other patents and patent applications suggest the use of Raf kinase inhibitors for treating leukemia (see, *e.g.*, U.S. Patent Nos. 6,268,391, and 6,204,467, and published U.S. Patent Application Nos. 20020137774; 20020082192; 20010016194; and 20010006975), or for treating breast cancer (see, *e.g.*, U.S. Patent Nos. 6,358,932, 5,717,100, 6,458,813, 6,268,391, and 6,204,467, and published U.S. Patent Application No. 20010014679).

Certain benzazole compounds and their use as Raf kinase inhibitors are disclosed in WO03082272 and published U.S. Patent Application No. 20040122237 A1. However, these published applications do not disclose the carboxamide compounds of the present invention.

SUMMARY OF THE INVENTION

New substituted benzazole compounds and pharmaceutically acceptable salts thereof or esters having a solubility enhancing moieties or prodrugs thereof are provided of the formula (I):



(I)

wherein, X_1 and X_3 are independently selected from N, -NR_4-, -O- or –S-, wherein R_4 is hydrogen or loweralkyl, provided that at least one of X_1 and X_3 must be N or -NR_4-;

X_2 is –NH- or $-(CH_2)_m-$, wherein m is 0, 1, 2, 3 or 4;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryllowerallkyl, heteroaryllowerallkyl, alkyloxy-alkylheterocyclolowerallkyl, or heteroaryllowerallkyl;

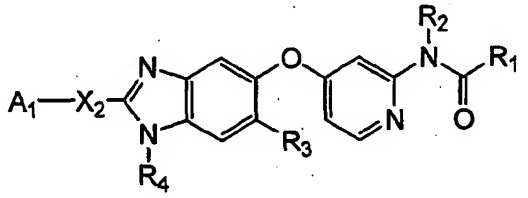
R_2 is hydrogen or loweralkyl;

each R_3 and R_3' are independently selected from hydrogen, halogen, hydroxy, cyano, loweralkyl, or loweralkoxy; and

p and q are independently 0, 1, 2 or 3; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other embodiments, new substituted benzimidazole compounds are provided of the formula (II):

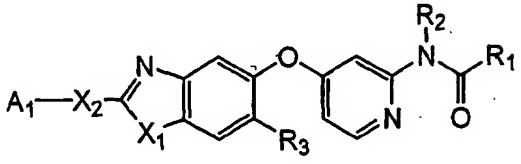


(II)

wherein and X_2, A_1, R_1, R_2, R_3, and R_4 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other embodiments, new substituted benzazole compounds are provided of the formula (III):

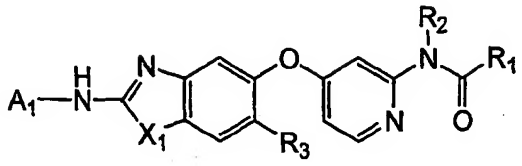


(III)

wherein and X_1, X_2, A_1, R_1, R_2, and R_3 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other embodiments, new substituted benzazole compounds are provided of the formula (IV):

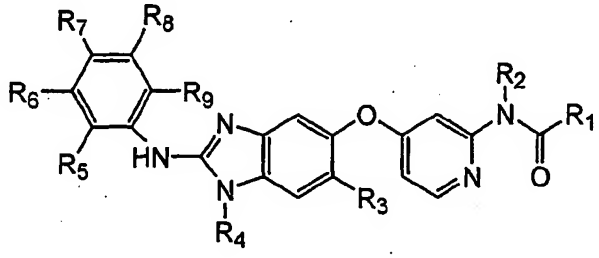


(IV)

wherein X_1, A_1, R_1, R_2, and R_3 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In yet other embodiments, new substituted benzimidazole compounds are provided of the formula (V):



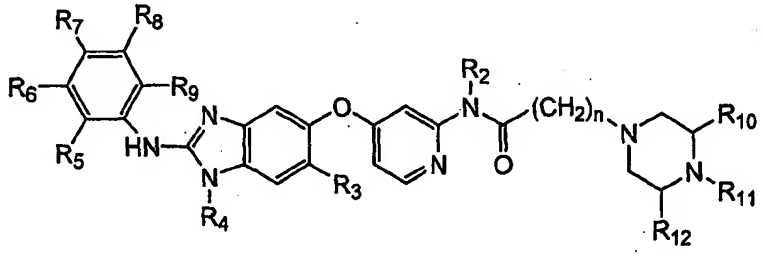
(V)

wherein R_1, R_2, R_3 and R_4 are as defined above; and

R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In yet other embodiments, new substituted benzimidazole compounds are provided of the formula (VI):



(VI)

wherein R_2, R_3, R_4 R_5, R_6, R_7, R_8 and R_9 are as defined above;

n is 0, 1, 2, 3 or 4;

R_{10}, and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

R_{11} is hydrogen, , loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV), (V) or (VI) effective to reduce or prevent tumor growth in the subject.

In yet other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV), (V) or (VI) effective to reduce or prevent tumor growth in the subject in combination with at least one additional agent for the treatment of cancer.

In yet other aspects, the present invention provides therapeutic compositions comprising at least one compound of formula (I), (II), (III), (IV), (V) or (VI) in combination with one or more additional agents for the treatment of cancer, as are commonly employed in cancer therapy.

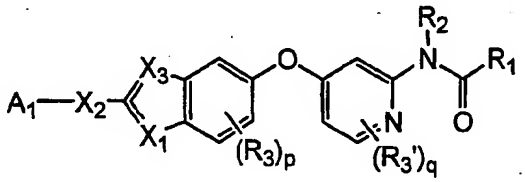
In yet other aspects, the present invention provides a compound of formula (I), (II), (III), (IV), (V) or (VI) for use as a pharmaceutical. The present invention further provides for the use of a compound of formula (I), (II), (III), (IV), (V) or (VI) in the manufacture of a medicament for the treatment of cancer.

The compounds of the invention are useful in the treatment of cancers, including malignant melanoma, papillary thyroid cancer, cholangiocarcinoma, gallbladder carcinoma, colorectal cancer, lung cancer, pancreatic cancer, leukemias, prostate cancer, ovarian cancer, breast cancer and lung cancer.

The invention further provides compositions, methods of use, and methods of manufacture as described in the detailed description of the invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

In accordance with one aspect of the present invention, new substituted benzazole compounds and pharmaceutically acceptable salts, esters or prodrugs thereof are provided of the formula (I):



(I)

wherein, X_1 and X_3 are independently selected from N, -NR_4-, -O- or –S-, wherein R_4 is hydrogen or loweralkyl, provided that at least one of X_1 and X_3 must be N or -NR_4-;

X_2 is –NH- or –$(CH_2)_m$- , wherein m is 0, 1, 2, 3 or 4;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryloweralkyl, heteroaryloweralkyl, alkyloxy-alkylheterocycloloweralkyl, or heteroaryloweralkyl;

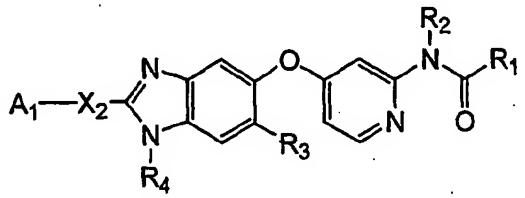
R_2 is hydrogen or loweralkyl;

each R_3 and R_3' are independently selected from hydrogen, halogen, hydroxy, cyano, loweralkyl, or loweralkoxy; and

p and q are independently 0, 1, 2 or 3; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In some aspects of the invention, X_1 in formula (I) is -NR_4-. Thus, in some embodiments, new substituted benzimidazole compounds are provided of the formula (II):

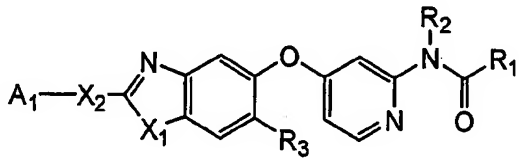


(II)

wherein and X_2, A_1, R_1, R_2, R_3, and R_4 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other embodiments of the invention, X_3 is N and X_4, is -CH- in formula (I). Thus, in some aspects the invention provides new substituted benzazole compounds of the formula (III):

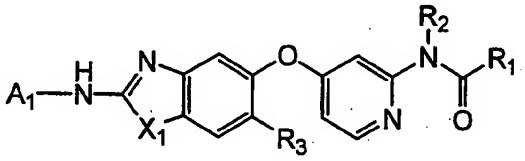


(III)

wherein and X_1, X_2, A_1, R_1, R_2, and R_3 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In other embodiments of the invention, X_2 is –NH- in formula (I). Thus, in some aspects, new substituted benzazole compounds are provided of the formula (IV):

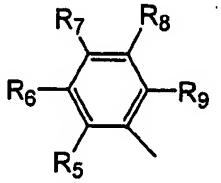


(IV)

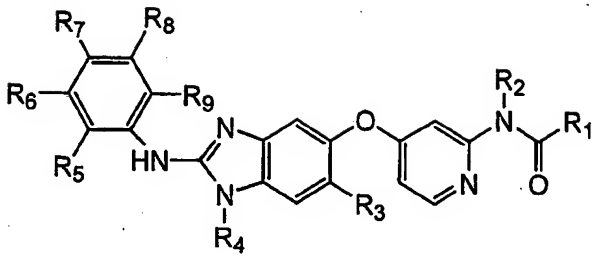
wherein X_1, A_1, R_1, R_2, and R_3 are as defined above; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In yet other embodiments of the invention, X_1 -NR_4-, X_2 is –NH-, X3 is N, X_4 is -CH- and A_1 is in formula (I) has the structure:



wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, halololoweralkyl, loweralkyloxy, halololoweralkyloxy, loweralkylthio, halololoweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. Thus, in some aspects, new substituted benzimidazole compounds are provided of the formula (V):



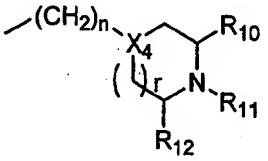
(V)

wherein R_1, R_2, R_3 and R_4 are as defined above; and

R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or

a pharmaceutically acceptable salt, ester or prodrug thereof. In representative, but non-limiting embodiments, R_5, R_6, R_7, R_8 and R_9 may be independently selected from, for example, hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

In yet other embodiments, R_1 in formula (V) has the structure:



wherein n is 0, 1, 2, 3 or 4;

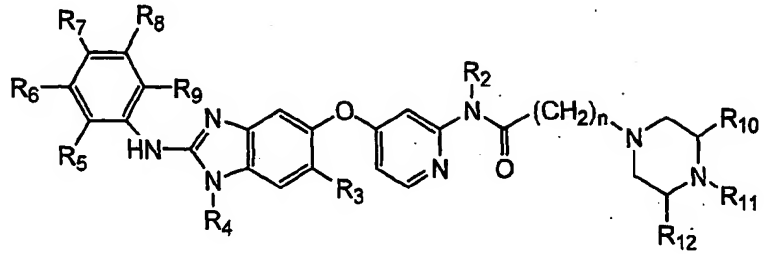
r is 1 or 2;

X_4 is –CH- or N

R_{10}, and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

R_{11} is hydrogen, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl. In some presently preferred embodiments, r is 1 and

X_4 is N. Thus, in some aspects the invention provides new substituted benzimidazole compounds are provided of the formula (VI):



(VI)

wherein R_2, R_3, R_4, R_5, R_6, R_7, R_8 and R_9 are as defined above;

n is 0, 1, 2, 3 or 4;

R_{10}, and R_{12} are independently selected from hydrogen, halo, loweralkyl, halologweralkyl, hydroxyloweralkyl, loweralkyloxy, halologweralkyloxy, loweralkyl-sulfonyl, halologweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

R_{11} is hydrogen, , loweralkyl, halologweralkyl, hydroxyloweralkyl, loweralkyloxy, halologweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

In another aspect, the present invention provides methods of treating human or animal subjects suffering from a Raf related disorder, such as cancer. Thus, the present invention provides methods of treating a human or animal subject in need of such treatment comprising administering to the subject a therapeutically effective amount of a compound of formula (I), (II), (III), (IV), (V) or (VI) above, either alone or in combination with other anticancer agents.

In other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject.

In yet other aspects, the present invention provides methods for treating Raf related disorders in a human or animal subject in need of such treatment comprising administering to said subject an amount of a compound of formula (I), (II), (III), (IV) or (V) effective to reduce or prevent tumor growth in the subject in combination with at

least one additional agent for the treatment of cancer. A number of suitable anticancer agents to be used as combination therapeutics are contemplated for use in the methods of the present invention. Indeed, the present invention contemplates, but is not limited to, administration of numerous anticancer agents such as: agents that induce apoptosis; polynucleotides (e.g., ribozymes); polypeptides (e.g., enzymes); drugs; biological mimetics; alkaloids; alkylating agents; antitumor antibiotics; antimetabolites; hormones; platinum compounds; monoclonal antibodies conjugated with anticancer drugs, toxins, and/or radionuclides; biological response modifiers (e.g. interferons [e.g. IFN-a, etc.] and interleukins [e.g. IL-2, etc.], etc.); adoptive immunotherapy agents; hematopoietic growth factors; agents that induce tumor cell differentiation (e.g. all-trans-retinoic acid, etc.); gene therapy reagents; antisense therapy reagents and nucleotides; tumor vaccines; inhibitors of angiogenesis, and the like. Numerous other examples of chemotherapeutic compounds and anticancer therapies suitable for coadministration with the disclosed compounds of formula (I), (II), (III), (IV), (V) or (VI) are known to those skilled in the art.

In preferred embodiments, anticancer agents to be used in combination with compounds of the present invention comprise agents that induce or stimulate apoptosis. Agents that induce apoptosis include, but are not limited to, radiation; kinase inhibitors (e.g., epidermal growth factor receptor [EGFR] kinase inhibitor, vascular endothelial growth factor receptor [VEGFR] kinase inhibitor, fibroblast growth factor receptor [FGFR] kinase inhibitor, platelet-derived growth factor receptor [PGFR] I kinase inhibitor, and Bcr-Abl kinase inhibitors such as Gleevec® [imatinib mesylate or STI-571]); antisense molecules; antibodies [e.g., Herceptin® anti-HER monoclonal antibody and Rituxan® anti-CD20 monoclonal antibody]; anti-estrogens [e.g., raloxifene and tamoxifen]; anti-androgens [e.g., flutamide, bicalutamide, finasteride, amino-glutethamide, ketoconazole, and corticosteroids]; cyclooxygenase 2 (COX-2) inhibitors [e.g., Celecoxib®, meloxicam, NS-398, and non-steroidal antiinflammatory drugs (NSAIDs)]; and cancer chemotherapeutic drugs [e.g., irinotecan (Camptosar®), CPT-11, fludarabine (Fludara®), dacarbazine (DTIC®), dexamethasone, mitoxantrone, Mylotarg®, VP-16, cisplatinum, 5-FU, doxrubicin, docetaxel (Taxotere® or taxol, dacarbazine, aldesleukin, capecitabine, and Iressa® (gefitinib)]; cellular signaling molecules; ceramides and cytokines; and staurosprine, and the like.

In some embodiments of this aspect of the invention, anticancer agents to be used in combination with compounds of the present invention include, for example, dacarbazine, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab

In other aspects, the present invention provides pharmaceutical compositions comprising at least one compound of formula I, II, III, IV or V together with a pharmaceutically acceptable carrier suitable for administration to a human or animal subject, either alone or together with other anticancer agents.

In other aspects, the present invention provides methods of manufacture of compounds of formula (I), (II), (III), (IV), (V) or (VI) as described herein.

In yet other aspects, the present invention provides compounds which are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of $p21^{ras}$, the instant inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase. In particular, the compounds are useful in the treatment of human or animal, e.g., murine cancer, since the progression of these cancers is dependent upon the ras protein signal transduction cascade and therefore is susceptible to treatment by interruption of the cascade by inhibiting raf kinase activity. Accordingly, the compounds of the invention are useful in treating cancers, such as, for example, malignant melanoma, papillary thyroid cancer, cholangiocarcinoma, gallbladder carcinoma, colorectal cancer, lung cancer, pancreatic cancer, leukemias, prostate cancer, ovarian cancer, breast cancer and lung cancer.

"Raf inhibitor" is used herein to refer to a compound that exhibits an IC_{50} with respect to Raf Kinase activity of no more than about 100 μM and more typically not more than about 50 μM, as measured in the Raf/Mek Filtration Assay described generally hereinbelow. Preferred isoforms of Raf Kinase in which the compounds of the present invention will be shown to inhibit, include A-Raf, B-Raf, and C-Raf (Raf-1). "IC_{50}" is that concentration of inhibitor which reduces the activity of an enzyme (e.g., Raf kinase) to half-maximal level. Representative compounds of the present invention have been discovered to exhibit inhibitory activity against Raf. Compounds of the present invention preferably exhibit an IC_{50} with respect to Raf of no more than about 10 μM, more preferably, no more than about 5 μM, even more preferably not more than about 1 μM,

and most preferably, not more than about 200 nM, as measured in the Raf kinase assays described herein.

As used herein, the term "benzazoles" includes benzimidazoles, benzothiazoles and benzoxazoles.

The phrase "alkyl" refers to alkyl groups that do not contain heteroatoms. Thus the phrase includes straight chain alkyl groups such as methyl, ethyl, propyl, butyl, pentyl, hexyl, heptyl, octyl, nonyl, decyl, undecyl, dodecyl and the like. The phrase also includes branched chain isomers of straight chain alkyl groups, including but not limited to, the following which are provided by way of example: $-CH(CH_3)_2$, $-CH(CH_3)(CH_2CH_3)$, $-CH(CH_2CH_3)_2$, $-C(CH_3)_3$, $-C(CH_2CH_3)_3$, $-CH_2CH(CH_3)_2$, $-CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH(CH_2CH_3)_2$, $-CH_2C(CH_3)_3$, $-CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_3)_2$, $-CH_2CH_2CH(CH_3)(CH_2CH_3)$, $-CH_2CH_2CH(CH_2CH_3)_2$, $-CH_2CH_2C(CH_3)_3$, $-CH_2CH_2C(CH_2CH_3)_3$, $-CH(CH_3)CH_2CH(CH_3)_2$, $-CH(CH_3)CH(CH_3)CH(CH_3)_2$, $-CH(CH_2CH_3)CH(CH_3)CH(CH_3)(CH_2CH_3)$, and others. The phrase also includes cyclic alkyl groups such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and cyclooctyl and such rings substituted with straight and branched chain alkyl groups as defined above. Thus the phrase alkyl groups includes primary alkyl groups, secondary alkyl groups, and tertiary alkyl groups. Preferred alkyl groups include straight and branched chain alkyl groups and cyclic alkyl groups having 1 to 12 carbon atoms.

As used herein "loweralkyl" includes both substituted or unsubstituted straight or branched chain alkyl groups having from 1 to 6 carbon atoms. Representative loweralkyl groups include, for example, methyl, ethyl, propyl, isopropyl, *n*-butyl, tert-butyl, neopentyl, trifluoromethyl, pentafluoroethyl and the like. Loweralkyl groups may be substituted, such as with halo, hydroxy, amino, nitro and/or cyano groups, and the like. Representative of halo-substituted and hydroxy-substituted loweralkyl include chloromethyl, trichloromethyl, fluoromethyl, trifluoromethyl, chloroethyl, fluoroethyl, hydroxyethyl, perfluoropentyl, perflurorheptyl and the like. Other suitable substituted loweralkyl moieties include, for example, aralkyl, aminoalkyl, aminoaralkyl, carbonylaminoalkyl, alkylcarbonylaminoalkyl, arylcarbonylaminoalkyl, aralkylcarbonyl-aminoalkyl, aminoalkoxyalkyl and arylaminoalkyl.

"Loweralkoxy" as used herein refers to RO- wherein R is loweralkyl. Representative examples of loweralkoxy groups include methoxy, ethoxy, *t*-butoxy, trifluoromethoxy and the like.

As used herein, the term "halogen" or "halo" refers to chloro, bromo, fluoro and iodo groups. "Haloalkyl" refers to an alkyl radical substituted with one or more halogen atoms. The term "halologweralkyl" refers to a loweralkyl radical substituted with one or more halogen atoms. The term "haloalkoxy" refers to an alkoxy radical substituted with one or more halogen atoms. The term "halologweralkoxy" refers to a loweralkoxy radical substituted with one or more halogen atoms.

"Amino" refers herein to the group $-NH_2$. The term "alkylamino" refers herein to the group –NRR' where R and R' are each independently selected from hydrogen or a lower alkyl. The term "arylamino" refers herein to the group –NRR' where R is aryl and R' is hydrogen, a lower alkyl, or an aryl. The term "aralkylamino" refers herein to the group –NRR' where R is a lower aralkyl and R' is hydrogen, a loweralkyl, an aryl, or a lowerarallkyl.

The term amino acid refers to both alpha and beta amino acids having D- or L-stereochemistry, and includes, but is not limited to, synthetic, non-natural amino acids having side chains other than those found in the 20 common amino acids. Non-natural amino acids are commercially available or may be prepared according to US 5,488,131 and references therein. Amino acids may be further substituted to contain modifications to their amino, carboxy, or side chain groups. These modifications include the numerous protecting groups commonly used in peptide synthesis.

The term "alkoxyalkyl" refers to the group $-alk_1-O-alk_2$ where alk_1 is alkyl or alkenyl, and alk_2 is alkyl or alkenyl. The term "loweralkoxyalkyl" refers to an alkoxyalkyl where alk_1 is loweralkyl or loweralkenyl, and alk_2 is loweralkyl or loweralkenyl. The term "aryloxyalkyl" refers to the group –alkyl-O-aryl. The term "aralkoxyalkyl" refers to the group -alkylenyl-O-aralkyl, where aralkyl is a lowerarallkyl.

The term "alkoxyalkylamino" refers herein to the group –NR-(alkoxyalkyl), where R is typically hydrogen, lowerarallkyl, or loweralkyl. The term "aminoloweralkoxyalkyl" refers herein to an aminoalkoxyalkyl in which the alkoxyalkyl is a loweralkoxyalkyl.

The term "aminocarbonyl" refers herein to the group $-C(O)-NH_2$. "Substituted aminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweralkyl and R' is

hydrogen or a loweralkyl. The term "arylaminocarbonyl" refers herein to the group -C(O)-NRR' where R is an aryl and R' is hydrogen, loweralkyl or aryl. "aralkylaminocarbonyl" refers herein to the group –C(O)-NRR' where R is loweraralkyl and R' is hydrogen, loweralkyl, aryl, or loweraralkyl.

"Aminosulfonyl" refers herein to the group $-S(O)_2-NH_2$. "Substituted aminosulfonyl" refers herein to the group $-S(O)_2$-NRR' where R is loweralkyl and R' is hydrogen or a loweralkyl. The term "aralkylaminosulfonlyaryl" refers herein to the group –aryl-$S(O)_2$–NH-aralkyl, where the aralkyl is loweraralkyl.

"Carbonyl" refers to the divalent group –C(O)-.

"Carbonyloxy" refers generally to the group –C(O)-O. Such groups include esters, -C(O)-O-R, where R is loweralkyl, cycloalkyl, aryl, or loweraralkyl. The term "carbonyloxycycloalkyl" refers generally herein to both a "carbonyloxycarbocycloalkyl" and a "carbonyloxyheterocycloalkyl", i.e., where R is a carbocycloalkyl or heterocycloalkyl, respectively. The term "arylcarbonyloxy" refers herein to the group –C(O)-O-aryl, where aryl is a mono- or polycyclic, carbocycloaryl or heterocycloaryl. The term "aralkylcarbonyloxy" refers herein to the group –C(O)-O-aralkyl, where the aralkyl is loweraralkyl.

The term "sulfonyl" refers herein to the group $-SO_2$-. "Alkylsulfonyl" refers to a substituted sulfonyl of the structure $-SO_2R$- in which R is alkyl. Alkylsulfonyl groups employed in compounds of the present invention are typically loweralkylsulfonyl groups having from 1 to 6 carbon atoms in its backbone structure. Thus, typical alkylsulfonyl groups employed in compounds of the present invention include, for example, methylsulfonyl (i.e., where R is methyl), ethylsulfonyl (i.e., where R is ethyl), propylsulfonyl (i.e., where R is propyl), and the like. The term "arylsulfonyl" refers herein to the group $-SO_2$-aryl. The term "aralkylsulfonyl" refers herein to the group -SO_2-aralkyl, in which the aralkyl is loweraralkyl. The term "sulfonamido" refers herein to $-SO_2NH_2$.

As used herein, the term "carbonylamino" refers to the divalent group -NH-C(O)- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced a loweralkyl, aryl, or loweraralkyl group. Such groups include moieties such as carbamate esters (-NH-C(O)-O-R) and amides –NH-C(O)-O-R, where R is a straight or branched chain loweralkyl, cycloalkyl, or aryl or loweraralkyl. The term "loweralkylcarbonylamino" refers to alkylcarbonylamino where R is a loweralkyl having

from 1 to about 6 carbon atoms in its backbone structure. The term "arylcarbonylamino" refers to group –NH-C(O)-R where R is an aryl. Similarly, the term "aralkylcarbonylamino " refers to carbonylamino where R is a lower aralkyl. As used herein, the term "aminocarbonyl" refers to the divalent group -C(O)-NH- in which the hydrogen atom of the amide nitrogen of the carbonylamino group can be replaced a loweralkyl, aryl, or loweraralkyl group, as described above.

As used herein, the term "guanidino" or "guanidyl" refers to moieties derived from guanidine, H_2N-C(=NH)-NH_2. Such moieties include those bonded at the nitrogen atom carrying the formal double bond (the "2"-position of the guanidine, e.g., diaminomethyleneamino, $(H_2N)_2C$=NH-) and those bonded at either of the nitrogen atoms carrying a formal single bond (the "1-" and/or "3"-positions of the guandine, e.g., H_2N-C(=NH)-NH-). The hydrogen atoms at any of the nitrogens can be replaced with a suitable substituent, such as loweralkyl, aryl, or loweraralkyl.

As used herein, the term "amidino" refers to the moieties R-C(=N)-NR′- (the radical being at the "N^1" nitrogen) and R(NR′)C=N- (the radical being at the "N^2" nitrogen), where R and R′ can be hydrogen, loweralkyl, aryl, or loweraralkyl.

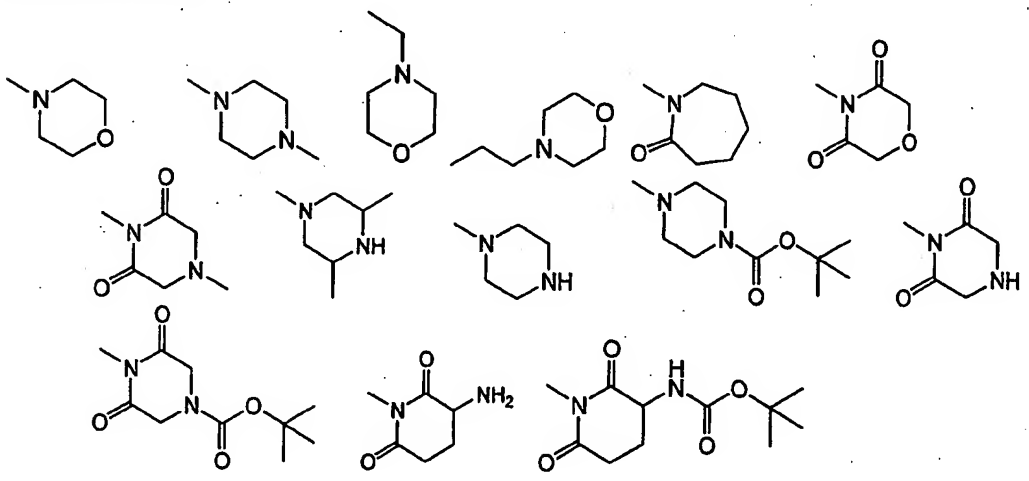
"Cycloalkyl" refers to a mono- or polycyclic, heterocyclic or carbocyclic alkyl substituent. Typical cycloalkyl substituents have from 3 to 8 backbone (i.e., ring) atoms in which each backbone atom is either carbon or a heteroatom. The term "heterocycloalkyl" refers herein to cycloalkyl substituents that have from 1 to 5, and more typically from 1 to 4 heteroatoms in the ring structure. Suitable heteroatoms employed in compounds of the present invention are nitrogen, oxygen, and sulfur. Representative heterocycloalkyl moieties include, for example, morpholino, piperazinyl, piperadinyl and the like. Carbocycloalkyl groups are cycloalkyl groups in which all ring atoms are carbon. When used in connection with cycloalkyl substituents, the term "polycyclic" refers herein to fused and non-fused alkyl cyclic structures. Examples of such polycyclic structures include bicyclic compounds having two bridgehead atoms connected by three or more arms. An example of a bicyclic structure is bicyclo[2.2.1] heptane, in which the bridgehead atoms are connected by three arms respectively having two, two, and one carbon atoms.

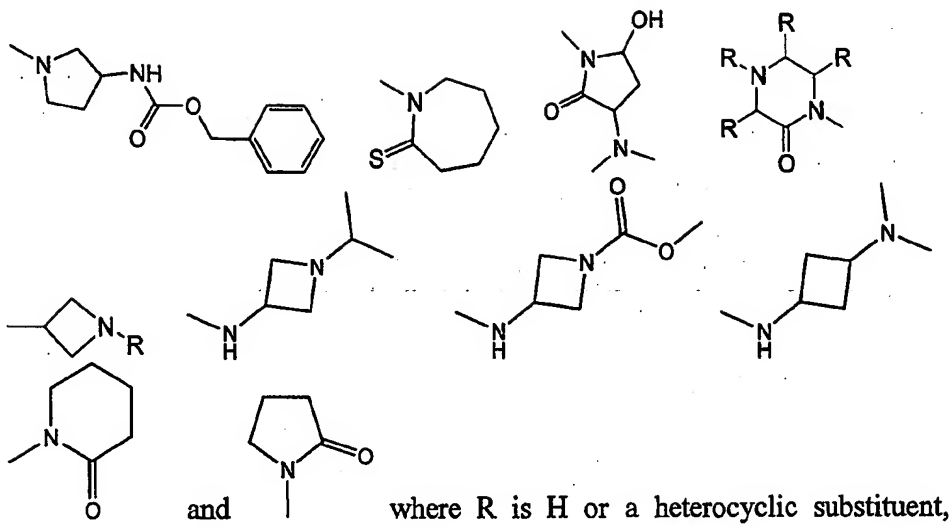
The term "substituted heterocycle" or "heterocyclic group" or heterocycle as used herein refers to any 3- or 4-membered ring containing a heteroatom selected from nitrogen, oxygen, and sulfur or a 5- or 6-membered ring containing from one to three

heteroatoms selected from the group consisting of nitrogen, oxygen, or sulfur; wherein the 5-membered ring has 0-2 double bonds and the 6-membered ring has 0-3 double bonds; wherein the nitrogen and sulfur atom maybe optionally oxidized; wherein the nitrogen and sulfur heteroatoms maybe optionally quarternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring or another 5- or 6-membered heterocyclic ring independently defined above. The term "heterocycle" thus includes rings in which nitrogen is the heteroatom as well as partially and fully-saturated rings. Preferred heterocycles include, for example: diazapinyl, pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazoyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, N-methyl piperazinyl, azetidinyl, N-methylazetidinyl, pyrimidinyl, pyridazinyl, oxazolyl, oxazolidinyl, isoxazolyl, isoazolidinyl, morpholinyl, thiazolyl, thiazolidinyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl, triazolyl and benzothienyl.

Heterocyclic moieties can be unsubstituted or monosubstituted or disubstituted with various substituents independently selected from hydroxy, halo, oxo (C=O), alkylimino (RN=, wherein R is a loweralkyl or loweralkoxy group), amino, alkylamino, dialkylamino, acylaminoalkyl, alkoxy, thioalkoxy, polyalkoxy, loweralkyl, cycloalkyl or haloalkyl.

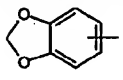
The heterocyclic groups may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.





and where R is H or a heterocyclic substituent, as described herein.

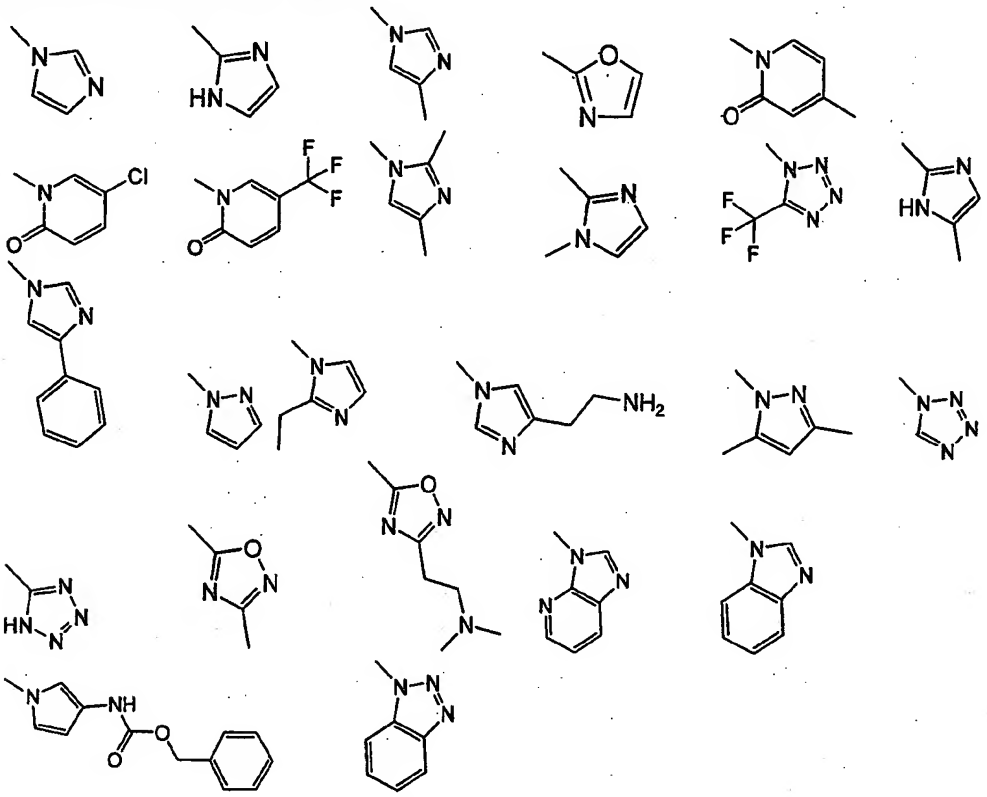
Representative heterocyclics include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, furanyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl, indolyl, naphthpyridinyl, indazolyl, and quinolizinyl.

"Aryl" refers to optionally substituted monocyclic and polycyclic aromatic groups having from 3 to 14 backbone carbon or hetero atoms, and includes both carbocyclic aryl groups and heterocyclic aryl groups. Carbocyclic aryl groups are aryl groups in which all ring atoms in the aromatic ring are carbon. The term "heteroaryl" refers herein to aryl groups having from 1 to 4 heteroatoms as ring atoms in an aromatic ring with the remainder of the ring atoms being carbon atoms. When used in connection with aryl substituents, the term "polycyclic aryl" refers herein to fused and non-fused cyclic structures in which at least one cyclic structure is aromatic, such as, for example, benzodioxozolo (which has a heterocyclic structure fused to a phenyl group, i.e.,  , naphthyl, and the like. Exemplary aryl moieties employed as substituents in compounds of the present invention include phenyl, pyridyl, pyrimidinyl, thiazolyl, indolyl, imidazolyl, oxadiazolyl, tetrazolyl, pyrazinyl, triazolyl, thiophenyl, furanyl, quinolinyl, purinyl, naphthyl, benzothiazolyl, benzopyridyl, and benzimidazolyl, and the like.

"Aralkyl" refers to an alkyl group substituted with an aryl group. Typically, aralkyl groups employed in compounds of the present invention have from 1 to 6 carbon atoms incorporated within the alkyl portion of the aralkyl group. Suitable aralkyl groups

employed in compounds of the present invention include, for example, benzyl, picolyl, and the like.

Representative heteroaryl groups include, for example, those shown below. These heteroaryl groups can be further substituted and may be attached at various positions as will be apparent to those having skill in the organic and medicinal chemistry arts in conjunction with the disclosure herein.



Representative heteroaryl groups include, for example, imidazolyl, pyridyl, piperazinyl, azetidinyl, thiazolyl, triazolyl benzimidazolyl, benzothiazolyl, benzoxazolyl, pyrazolyl and pyrazinyl.

The term "biaryl" refers to a group or substituent to which two aryl groups, which are not condensed to each other, are bound. Exemplary biaryl compounds include, for example, phenylbenzene, diphenyldiazene, 4-methylthio-1-phenylbenzene, phenoxy-benzene, (2-phenylethynyl)benzene, diphenyl ketone, (4-phenylbuta-1,3-diynyl)benzene, phenylbenzylamine, (phenylmethoxy)benzene, and the like. Preferred optionally substituted biaryl groups include: 2-(phenylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 1,4-diphenylbenzene, N-[4-(2-phenylethynyl)phenyl]-2-[benzylamino]acetamide, 2-amino-N-[4-(2-phenylethynyl)phenyl]propanamide, 2-amino-N-[4-(2-phenylethynyl)-phenyl]acetamide, 2-(cyclopropylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-

(ethylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-[(2-methylpropyl)amino]-N-[4-(2-phenylethynyl)phenyl]acetamide, 5-phenyl-2H-benzo[d]1,3-dioxolene, 2-chloro-1-methoxy-4-phenylbenzene, 2-[(imidazolylmethyl)amino]-N-[4-(2-phenylethynyl)phenyl]-acetamide, 4-phenyl-1-phenoxybenzene, N-(2-aminoethyl)[4-(2-phenylethynyl)phenyl]-carboxamide, 2-{[(4-fluorophenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-{[(4-methylphenyl)methyl]amino}-N-[4-(2-phenylethynyl)phenyl]acetamide, 4-phenyl-1-(trifluoromethyl)benzene, 1-butyl-4-phenylbenzene, 2-(cyclohexylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, 2-(ethylmethylamino)-N-[4-(2-phenylethynyl)-phenyl]acetamide, 2-(butylamino)-N-[4-(2-phenylethynyl)phenyl]acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(4-pyridylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]-2-(quinuclidin-3-ylamino)acetamide, N-[4-(2-phenylethynyl)phenyl]pyrrolidin-2-ylcarboxamide, 2-amino-3-methyl-N-[4-(2-phenylethynyl)phenyl]butanamide, 4-(4-phenylbuta-1,3-diynyl)phenylamine, 2-(dimethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]-acetamide, 2-(ethylamino)-N-[4-(4-phenylbuta-1,3-diynyl)phenyl]acetamide, 4-ethyl-1-phenylbenzene, 1-[4-(2-phenylethynyl)phenyl]ethan-1-one, N-(1-carbamoyl-2-hydroxy-propyl)[4-(4-phenylbuta-1,3-diynyl)phenyl]carboxamide, N-[4-(2-phenylethynyl)-phenyl]propanamide, 4-methoxyphenyl phenyl ketone, phenyl-N-benzamide, (tert-butoxy)-N-[(4-phenylphenyl)methyl]carboxamide, 2-(3-phenylphenoxy)ethane-hydroxamic acid, 3-phenylphenyl propanoate, 1-(4-ethoxyphenyl)-4-methoxybenzene, and [4-(2-phenylethynyl)phenyl]pyrrole.

The term "heteroarylaryl" refers to a biaryl group where one of the aryl groups is a heteroaryl group. Exemplary heteroarylaryl groups include, for example, 2-phenylpyridine, phenylpyrrole, 3-(2-phenylethynyl)pyridine, phenylpyrazole, 5-(2-phenylethynyl)-1,3-dihydropyrimidine-2,4-dione, 4-phenyl-1,2,3-thiadiazole, 2-(2-phenylethynyl)pyrazine, 2-phenylthiophene, phenylimidazole, 3-(2-piperazinylphenyl)-furan, 3-(2,4-dichlorophenyl)-4-methylpyrrole, and the like. Preferred optionally substituted heteroarylaryl groups include: 5-(2-phenylethynyl)pyrimidine-2-ylamine, 1-methoxy-4-(2-thienyl)benzene, 1-methoxy-3-(2-thienyl)benzene, 5-methyl-2-phenyl-pyridine, 5-methyl-3-phenylisoxazole, 2-[3-(trifluoromethyl)phenyl]furan, 3-fluoro-5-(2-furyl)-2-methoxy-1-prop-2-enylbenzene, (hydroxyimino)(5-phenyl(2-thienyl))-methane, 5-[(4-methylpiperazinyl)methyl]-2-phenylthiophene, 2-(4-ethylphenyl)thio-phene, 4-methylthio-1-(2-thienyl)benzene, 2-(3-nitrophenyl)thiophene, (tert-butoxy)-N-

[(5-phenyl(3-pyridyl))methyl]carboxamide, hydroxy-N-[(5-phenyl(3-pyridyl))methyl]-amide, 2-(phenylmethylthio)pyridine, and benzylimidazole.

The term "heteroarylheteroaryl" refers to a biaryl group where both of the aryl groups are a heteroaryl group. Exemplary heteroarylheteroaryl groups include, for example, 3-pyridylimidazole, 2-imidazolylpyrazine, and the like. Preferred optionally substituted heteroarylheteroaryl groups include: 2-(4-piperazinyl-3-pyridyl)furan, diethyl-(3-pyrazin-2-yl(4-pyridyl))amine, and dimethyl{2-[2-(5-methylpyrazin-2-yl)ethynyl](4-pyridyl)}amine.

"Optionally substituted" or "substituted" refers to the replacement of one or more hydrogen atoms with a monovalent or divalent radical. Suitable substitution groups include, for example, hydroxyl, nitro, amino, imino, cyano, halo, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, halologweralkyl, loweralkyamino, halologweralkylamino, loweralkoxy, halologweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, arylcarbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like. The term substituted and unsubstituted, when introducing a list of substituents, is intended to apply to each member of that list. For instance the phrase "substituted and unsubstituted aryl, heteroaryl, or alkyl" and the phrase "substituted and unsubstituted aryl, heteroaryl, and alkyl" is intended to specify aryl, heteroaryl, and alky groups that are each substituted or unsubstituted.

The substitution group can itself be substituted. The group substituted onto the substitution group can be carboxyl, halo; nitro, amino, cyano, hydroxyl, loweralkyl, loweralkoxy, aminocarbonyl, -SR, thioamido, $-SO_3H$, $-SO_2R$ or cycloalkyl, where R is typically hydrogen, hydroxyl or loweralkyl.

When the substituted substituent includes a straight chain group, the substitution can occur either within the chain (e.g., 2-hydroxypropyl, 2-aminobutyl, and the like) or at the chain terminus (e.g., 2-hydroxyethyl, 3-cyanopropyl, and the like). Substituted substitutents can be straight chain, branched or cyclic arrangements of covalently bonded carbon or heteroatoms.

As used herein, the term "carboxy-protecting group" refers to a carbonyl group which has been esterified with one of the commonly used carboxylic acid protecting ester groups employed to block or protect the carboxylic acid function while reactions

involving other functional sites of the compound are carried out. In addition, a carboxy protecting group can be attached to a solid support whereby the compound remains connected to the solid support as the carboxylate until cleaved by hydrolytic methods to release the corresponding free acid. Representative carboxy-protecting groups include, for example, loweralkyl esters, secondary amides and the like.

As used herein, the term "pharmaceutically acceptable salts" refers to the nontoxic acid or alkaline earth metal salts of the compounds of Formula I. These salts can be prepared *in situ* during the final isolation and purification of the compounds of Formula I, or by separately reacting the base or acid functions with a suitable organic or inorganic acid or base, respectively. Representative salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-napthalenesulfonate, oxalate, pamoate, pectinate, persulfate, 3-phenylproionate, picrate, pivalate, propionate, succinate, sulfate, tartrate, thiocyanate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as loweralkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulfuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, methanesulfonic acid, succinic acid and citric acid. Basic addition salts can be prepared *in situ* during the final isolation and purification of the compounds of formula (I), or separately by reacting carboxylic acid moieties with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia, or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on the alkali and alkaline earth metals, such as sodium, lithium, potassium, calcium, magnesium, aluminum salts and the like, as well as

nontoxic ammonium, quaternary ammonium, and amine cations, including, but not limited to ammonium, tetramethylammonium, tetraethylammonium, methylamine, dimethylamine, trimethylamine, triethylamine, ethylamine, and the like. Other representative organic amines useful for the formation of base addition salts include diethylamine, ethylenediamine, ethanolamine, diethanolamine, piperazine and the like.

As used herein, the term "pharmaceutically acceptable ester" refers to esters, which hydrolyze *in vivo* and include those that break down readily in the human body to leave the parent compound or a salt thereof. Suitable ester groups include, for example, those derived from pharmaceutically acceptable aliphatic carboxylic acids, particularly alkanoic, alkenoic, cycloalkanoic and alkanedioic acids, in which each alkyl or alkenyl moiety advantageously has not more than 6 carbon atoms. Examples of particular esters include formates, acetates, propionates, butyrates, acrylates and ethylsuccinates.

The term "pharmaceutically acceptable prodrugs" as used herein refers to those prodrugs of the compounds of the present invention which are, within the scope of sound medical judgment, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio, and effective for their intended use, as well as the zwitterionic forms, where possible, of the compounds of the invention. The term "prodrug" refers to compounds that are rapidly transformed *in vivo* to yield the parent compound of the above formula, for example by hydrolysis in blood. A thorough discussion is provided in T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference.

The term "cancer" refers to cancer diseases that can be beneficially treated by the inhibition of Raf kinase, including, for example, cancers such as malignant melanoma, papillary thyroid cancer, cholangiocarcinoma, gallbladder carcinoma, colorectal cancer, lung cancer, pancreatic cancer, leukemias, prostate cancer, ovarian cancer, breast cancer and lung cancer.

In illustrative embodiments of the invention, A_1 may be, for example, phenyl, phenylalkyl, pyridyl, pyrimidinyl, pyridylalkyl, pyrimidinylalkyl, alkylbenzoate, thiophene, thiophene-2-carboxylate, indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, morpholinyl, N-piperazinyl, N-

morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, napththalenyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-fluoren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, furanyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, and 1,4'-bipiperidin-1'-yl, which may be substituted by one or more substitutents selected from the group consisting of hydroxyl, nitro, cyano, halo, and substituted or unsubstituted amino, imino, thio, sulfonyl, thioamido, amidino, imidino, oxo, oxamidino, methoxamidino, imidino, guanidino, sulfonamido, carboxyl, formyl, loweralkyl, haloloweralkyl, loweralkyamino, haloloweralkylamino, loweralkoxy, halooloweralkoxy, loweralkoxyalkyl, alkylcarbonyl, aminocarbonyl, loweralkylaminocarbonyl, heterocycloalkylloweralkylaminocarbonyl, carboxylloweralkylaminocarbonyl, aryl-carbonyl, aralkylcarbonyl, heteroarylcarbonyl, heteroaralkylcarbonyl, alkylthio, aminoalkyl, cyanoalkyl, aryl and the like. In other embodiments, A_1 may be substituted phenyl, such as, for example, substituted or unsubstituted hydroxyphenyl, hydroxyalkylphenyl, alkylphenyl, dialkylphenyl, trialkylphenyl, alkoxyphenyl, dialkoxyphenyl, alkoxyalkylphenyl, halophenyl, dihalophenyl, haloalkylphenyl, haloalkoxyphenyl, alkylhalophenyl, alkoxyhalophenyl, alkylthiophenyl, aminophenyl, nitrophenyl, acetylphenyl, sulfamoylphenyl, biphenyl, alkoxybiphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, morpholinylphenyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkylphenyl, furanylphenyl, (1,4'-bipiperidin-1'-ylcarbonyl)phenyl, pyrimidin-5-ylphenyl, and quinolidinylphenyl. In yet other embodiments, A_1 is substituted phenyl selected from the group consisting of chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, dichlorophenyl, difluorophenyl, dibromophenyl, fluororchlorophenyl, bromochlorophenyl, trifluoromethylphenyl, trifluoromethoxyphenyl, alkylbromophenyl, trifluoromethylbromophenyl, alkyl-chlorophenyl, trifluoromethylchlorophenyl, alkylfluorophenyl, and trifluoromethyl-fluorophenyl.

In representative embodiments of the invention, the compounds of the invention include, for example, 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1H-benz-

imidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, 4-({2-[(3-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)-amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(3-chloro-4-fluorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-{[2-(phenylamino)-1H-benzimidazol-6-yl]oxy}pyridine-2-carboxamide, 4-[(2-{[4-bromo-2-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2-methylpropyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-[(2-{[4-(dimethylamino)naphthalen-1-yl]-amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(4-nitrophenyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, N-methyl-4-({2-[(phenylcarbonyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, N-methyl-4-({2-[(phenylmethyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, methyl 4-{[6-({2-[(methylamino)carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}benzoate, 4-({2-[(4-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-[(2-{[2-(ethyloxy)phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2-morpholin-4-ylethyl)-amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-({2-[(4-iodophenyl)-amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-[(2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-6-yl)oxy]pyridine-2-carboxamide, 4-({2-[(furan-2-ylmethyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-bromo-3-methylphenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(4-acetylphenyl)amino]-1H-benzimidazol-6-yl}-oxy)-N-methylpyridine-2-carboxamide, N-methyl-4-({2-[(2,4,6-trimethylphenyl)amino]-1H-benzimidazol-6-yl}oxy)pyridine-2-carboxamide, 4-[(2-{[4-(1,1-dimethylethyl)-phenyl]amino}-1H-benzimidazol-6-yl)oxy]-N-methylpyridine-2-carboxamide, 4-({2-[(2-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(3-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, 4-({2-[(2-chlorophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-methylpyridine-2-carboxamide, methyl 3-{[6-({2-[(methylamino)carbonyl]pyridin-4-yl}oxy)-1H-benzimidazol-2-yl]amino}thiophene-2-carboxylate, 4-({2-[(4-bromophenyl)amino]-1H-benzimidazol-6-yl}oxy)-N-{(3R,5R)-5-[(methyloxy)methyl]pyrrolidin-3-yl}pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-methylpyridine-2-carboxamide, 4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-

methyl-1H-benzimidazol-5-yl)oxy]-N-methylpyridine-2-carboxamide, N-methyl-4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-ethylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-hydroxyethyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N,N-dimethylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2,2,2-trifluoroethyl)pyridine-2-carboxamide, N-(4-bromophenyl)-1-methyl-5-{[2-(pyrrolidin-1-ylcarbonyl)pyridin-4-yl]oxy}-1H-benzimidazol-2-amine, ethyl (3R)-3-(methyloxy)-4-[({4-[(2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-carbonyl)amino]piperidine-1-carboxylate, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[2-(dimethylamino)ethyl]pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(tetrahydrofuran-2-ylmethyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(2-morpholin-4-ylethyl)pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(piperidin-4-ylmethyl)pyridine-2-carboxamide, 5-({2-[(3-aminopyrrolidin-1-yl)carbonyl]pyridin-4-yl}oxy)-N-(4-bromophenyl)-1-methyl-1H-benzimidazol-2-amine, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[1-(diphenylmethyl)azetidin-3-yl]pyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-piperidin-3-ylpyridine-2-carboxamide, 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-(1,3-thiazol-2-yl)pyridine-2-carboxamide, and 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-N-[(1-ethylpyrrolidin-2-yl)-methyl]pyridine-2-carboxamide, (4-{2-[(4-bromophenyl)amino]benzothiazol-5-yloxy}(2-pyridyl))-N-methylcarboxamide, (4-{2-[(4-bromophenyl)amino]benzoxazol-5-yloxy}-(2-pyridyl))-N-methylcarboxamide, and other representative compounds set forth in the Examples.

In other aspects, the present invention relates to the processes for preparing the compounds of Formulas (I), (II), (III), (IV), (V) and (VI) and to the synthetic intermediates useful in such processes.

The compounds of the invention comprise asymmetrically substituted carbon atoms. Such asymmetrically substituted carbon atoms can result in the compounds of the invention comprising mixtures of stereoisomers at a particular asymmetrically substituted

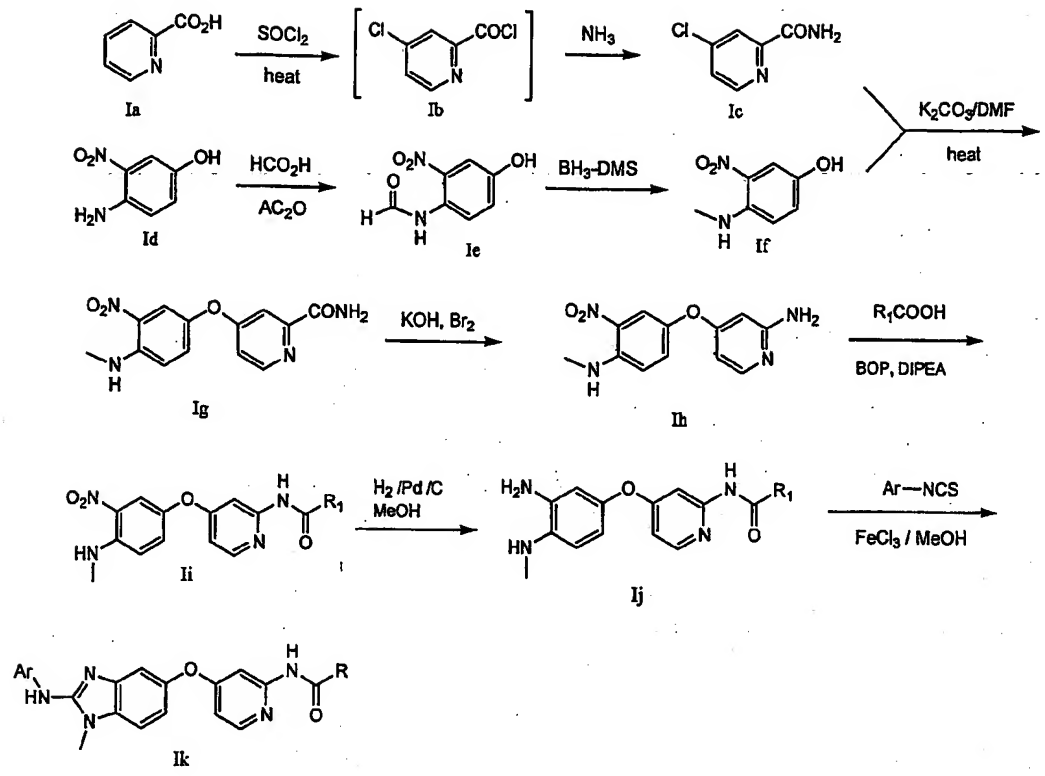
carbon atom or a single stereoisomer. As a result, racemic mixtures, mixtures of diastereomers, as well as single diastereomers of the compounds of the invention are included in the present invention. The terms "S" and "R" configuration, as used herein, are as defined by the IUPAC 1974 RECOMMENDATIONS FOR SECTION E, FUNDAMENTAL STEREOCHEMISTRY, *Pure Appl. Chem.* **45**:13-30 (1976). The terms α and β are employed for ring positions of cyclic compounds. The α-side of the reference plane is that side on which the preferred substituent lies at the lower numbered position. Those substituents lying on the opposite side of the reference plane are assigned β descriptor. It should be noted that this usage differs from that for cyclic stereoparents, in which "α" means "below the plane" and denotes absolute configuration. The terms α and β configuration, as used herein, are as defined by the CHEMICAL ABSTRACTS INDEX GUIDE-APPENDIX IV (1987) paragraph 203.

The present invention also relates to the processes for preparing the compounds of the invention and to the synthetic intermediates useful in such processes, as described in detail below.

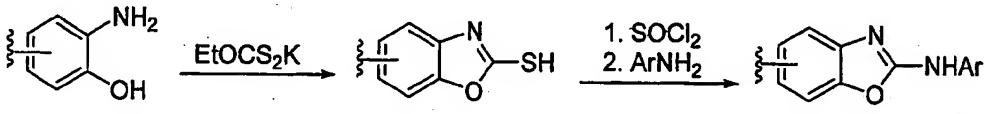
Synthetic Methods

Compounds of the invention containing a benzimidazole core may be prepared *via* a number of synthetic routes using methods familiar to one of skill in the art, such as those disclosed in WO03082272 and published U.S. Patent Application No. 20040122237 A1. One such route is as shown in Scheme I below. The pyridyl ether **Ig** is formed by coupling 4-halopyridine **Ic** with phenol **If** under basic conditions. The resulting amide **Ig** is treated with KOH and bromine to form the pyridyl amine **Ih** that may then be coupled with various acids to form amide **Ii**. Reduction of **Ii** gives diamine **Ij**, which may be coupled with various thioisocyanates to form benzimidazole **Ik**.

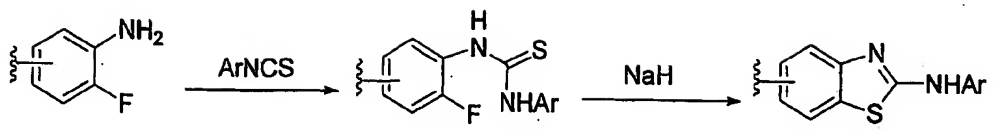
Scheme I



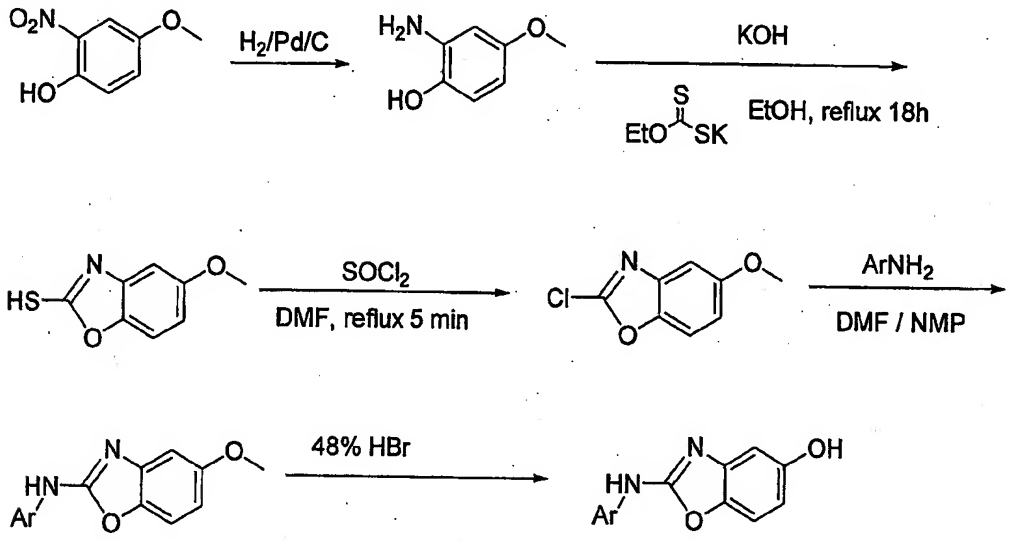
Compounds containing the oxazole structure may similarly be prepared according to the methods above or according to other known general procedures, such as those disclosed in WO03082272 and published U.S. Patent Application No. 20040122237 A1. In addition, Haviv et al. (*J. Med. Chem.* 1988, 31:1719) describes a procedure for assembling oxazole cores wherein a hydroxy aniline is treated with ethyl potassium xanthate. The resulting sulfuryl benzoxazole may then be chlorinated and coupled with an amine.



Compounds containing a benzothiazole core may also be prepared according to known methods, such as those disclosed in WO03082272 and published U.S. Patent Application No. 20040122237 A1. An ortho-haloamine may be reacted with a thioisocyanate to form a thiourea. Reduction with NaH then allows formation of the thiazole ring.



Intermediates for synthesizing benzoxazoles may generally be prepared through the following pathway:



The compounds of the invention are useful *in vitro* or *in vivo* in inhibiting the growth of cancer cells. The compounds may be used alone or in compositions together with a pharmaceutically acceptable carrier or excipient. Suitable pharmaceutically acceptable carriers or excipients include, for example, processing agents and drug delivery modifiers and enhancers, such as, for example, calcium phosphate, magnesium stearate, talc, monosaccharides, disaccharides, starch, gelatin, cellulose, methyl cellulose, sodium carboxymethyl cellulose, dextrose, hydroxypropyl-β-cyclodextrin, polyvinyl-pyrrolidinone, low melting waxes, ion exchange resins, and the like, as well as combinations of any two or more thereof. Other suitable pharmaceutically acceptable excipients are described in "Remington's Pharmaceutical Sciences," Mack Pub. Co., New Jersey (1991), incorporated herein by reference.

Effective amounts of the compounds of the invention generally include any amount sufficient to detectably inhibit Raf activity by any of the assays described herein, by other Raf kinase activity assays known to those having ordinary skill in the art or by detecting an inhibition or alleviation of symptoms of cancer.

The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy. The therapeutically effective amount for a given situation can be readily determined by routine experimentation and is within the skill and judgment of the ordinary clinician.

For purposes of the present invention, a therapeutically effective dose will generally be a total daily dose administered to a host in single or divided doses may be in amounts, for example, of from 0.001 to 1000 mg/kg body weight daily and more preferred from 1.0 to 30 mg/kg body weight daily. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

The compounds of the present invention may be administered orally, parenterally, sublingually, by aerosolization or inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of transdermal administration such as transdermal patches or ionophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparations, for example, sterile injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-propanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or di-glycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols,

which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as is normal practice, additional substances other than inert diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

Liquid dosage forms for oral administration may include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, emulsifying and suspending agents, cyclodextrins, and sweetening, flavoring, and perfuming agents.

The compounds of the present invention can also be administered in the form of liposomes. As is known in the art, liposomes are generally derived from phospholipids or other lipid substances. Liposomes are formed by mono- or multi-lamellar hydrated liquid crystals that are dispersed in an aqueous medium. Any non-toxic, physiologically acceptable and metabolizable lipid capable of forming liposomes can be used. The present compositions in liposome form can contain, in addition to a compound of the present invention, stabilizers, preservatives, excipients, and the like. The preferred lipids are the phospholipids and phosphatidyl cholines (lecithins), both natural and synthetic. Methods to form liposomes are known in the art. See, for example, Prescott, Ed., *Methods in Cell Biology*, Volume XIV, Academic Press, New York, N.W., p. 33 *et seq.* (1976).

While the compounds of the invention can be administered as the sole active pharmaceutical agent, they can also be used in combination with one or more other agents used in the treatment of cancer. Representative agents useful in combination with the compounds of the invention for the treatment of cancer include, for example, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib (Gleevec), anthracyclines, rituximab, trastuzumab, as well as other cancer chemotherapeutic agents.

The above compounds to be employed in combination with the compounds of the invention will be used in therapeutic amounts as indicated in the *Physicians' Desk Reference* (PDR) 47th Edition (1993), which is incorporated herein by reference, or such therapeutically useful amounts as would be known to one of ordinary skill in the art.

The compounds of the invention and the other anticancer agents can be administered at the recommended maximum clinical dosage or at lower doses. Dosage levels of the active compounds in the compositions of the invention may be varied so as to obtain a desired therapeutic response depending on the route of administration, severity of the disease and the response of the patient. The combination can be administered as separate compositions or as a single dosage form containing both agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions, which are given at the same time or different times, or the therapeutic agents, can be given as a single composition.

Antiestrogens, such as tamoxifen, inhibit breast cancer growth through induction of cell cycle arrest, that requires the action of the cell cycle inhibitor p27Kip. Recently, it has been shown that activation of the Ras-Raf-MAP Kinase pathway alters the phosphorylation status of p27Kip such that its inhibitory activity in arresting the cell cycle is attenuated, thereby contributing to antiestrogen resistance (Donovan et al, *J. Biol. Chem. 276*:40888, 2001). As reported by Donovan et al., inhibition of MAPK signaling through treatment with MEK inhibitor changed the phosphorylation status of p27 in hormone refactory breast cancer cell lines and in so doing restored hormone sensitivity. Accordingly, in one aspect, the compounds of formulas (I), (II), (III), (IV) and (V) may be used in the treatment of hormone dependent cancers, such as breast and prostate cancers, to reverse hormone resistance commonly seen in these cancers with conventional anticancer agents.

In hematological cancers, such as chronic myelogenous leukemia (CML), chromosomal translocation is responsible for the constitutively activated BCR-AB1 tyrosine kinase. The afflicted patients are responsive to Gleevec, a small molecule tyrosine kinase inhibitor, as a result of inhibition of Ab1 kinase activity. However, many patients with advanced stage disease respond to Gleevec initially, but then relapse later due to resistance-conferring mutations in the Ab1 kinase domain. *In vitro* studies have demonstrated that BCR-Av1 employs the Raf kinase pathway to elicit its effects. In addition, inhibiting more than one kinase in the same pathway provides additional

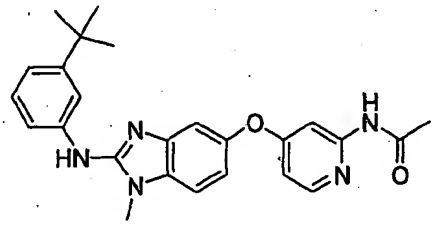
protection against resistance-conferring mutations. Accordingly, in another aspect of the invention, the compounds of formulas (I), (II), (III), (IV) and (V) are used in combination with at least one additional agent, such as Gleevec, in the treatment of hematological cancers, such as chronic myelogenous leukemia (CML), to reverse or prevent resistance to the at least one additional agent.

The present invention will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

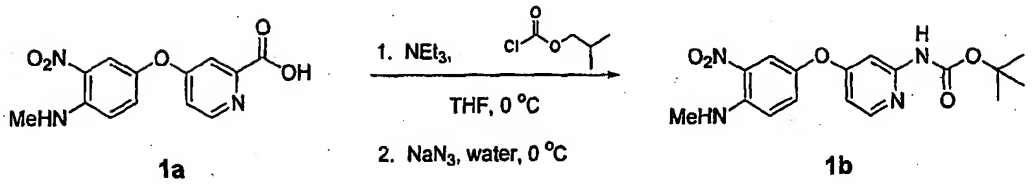
Representative side chains for use in the compounds of the following examples may generally be prepared in accordance with the following procedures:

Example 1

Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



Step 1:



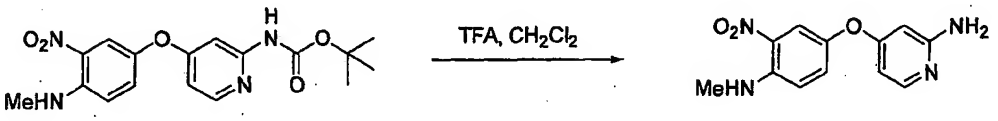
1a 1b

Triethylamine (5 mL, 35.6 mmol) was added to a stirring suspension of acid **1a** (3.34 g, 11.6 mmol) in dry THF (44 mL) at 0 °C. The reaction was maintained at 0 °C for 1 h, after which a solution of *iso*butylchloroformate (1.8 mL, 13.9 mmol) in dry THF (14 mL) was added dropwise. After 1 h at 0 °C, a solution of sodium azide (2.28 g, 35.1 mmol) in water (8 mL) was added and the resulting reaction was maintained at 0 °C for

45 min. The reaction solution was concentrated into an aqueous slurry and partitioned between saturated aqueous $NaHCO_3$ solution and CH_2Cl_2. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (3 X). The combined organics were washed with brine and the combined aqueous portions were further extracted with CH_2Cl_2. The combined organic phases were dried ($MgSO_4$) and concentrated to give 2.71 g (8.6 mmol, 75%) of an orange solid as crude acyl azide.

A suspension of acyl azide (322 mg, 1.02 mol) and *t*-butanol (0.2 mL, 2.09 mmol) in dry toluene (12 mL) was heated to 100 °C and maintained at that temperature for 1.5 h. The reaction was allowed to cool to rt and then partitioned between saturated aqueous Na_2CO_3 solution and CH_2Cl_2. The phases were separated and the aqueous portion was extracted with CH_2Cl_2 (3 X). The combined organic portions were washed with saturated aqueous Na_2CO_3 solution (2 X) and brine, dried ($MgSO_4$), and adsorbed onto SiO_2. Purification by flash chromatography (9 : 1, 4 : 1, 2 : 1 hexanes-EtOAc) afforded 131 mg (0.36 mmol, 36%) of an orange solid as **1b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (br s, 1 H), 8.12 (d, J = 5.8 Hz, 1 H), 8.04 (br dd, 1 H), 7.95 (d, J = 2.8 Hz, 1 H), 7.53 (d, J = 2.2, 1 H), 7.29 (dd, J = 2.8, 9.1 Hz, 1 H), 6.91 (d, J = 9.3 Hz, 1 H), 6.47 (dd, J = 2.5, 5.8 Hz, 1 H), 3.07 (d, J = 5.2 Hz, 3 H), 1.49 (s, 9 H).

Step 2:

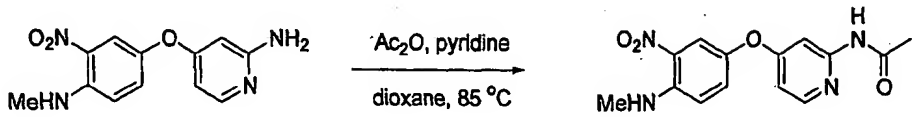


1b **1c**

Trifluoroacetic acid (4 mL) was added to a stirring suspension of BOC carbamate **1b** (181 mg, 0.5 mmol) in CH_2Cl_2 (4 mL). The resulting reaction was maintained at rt for 3.5 h and was then concentrated. The crude residue was suspended in saturated aqueous Na_2CO_3 and extracted with CH_2Cl_2 (3 X). The combined organic portions were concentrated and the resulting residue was adsorbed onto SiO_2. Purification by flash chromatography (0.5 : 99.5, 0.75 : 99.25, 1 : 99, 2 : 98, 5 : 95 methanol-CH_2Cl_2) gave 94 mg (0.36 mmol, 72%) of a bright orange solid as **1c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (br d, J = 3.3 Hz, 1 H), 7.93 (d, J = 2.8 Hz, 1 H), 7.92 (d, J = 5.8 Hz, 1 H), 7.27 (dd, J =

2.8, 9.4 Hz, 1 H), 6.89 (d, J = 9.3 Hz, 1 H), 6.24 (dd, J = 2.2, 6.0 Hz, 1 H), 5.92 (d, J = 2.2 Hz, 1 H), 4.44 (br s, 2 H), 3.05 (d, J = 5.0 Hz, 3 H).

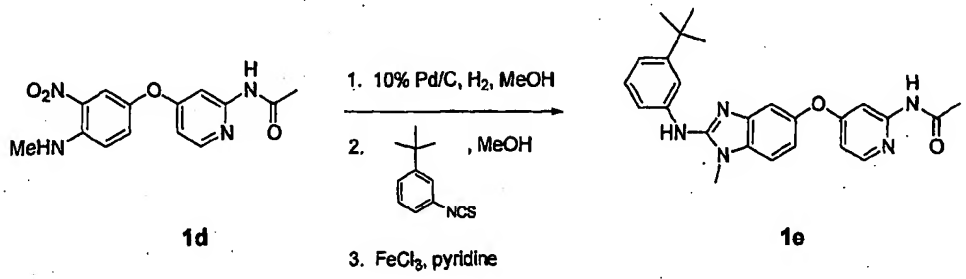
Step 3:



1c **1d**

Pyridine (0.08 mL, 0.99 mmol) and acetic anhydride (0.04 mL, 0.42 mmol) was added to suspension of 2-aminopyridine **1c** (94 mg, 0.36 mmol) in dry dioxane (1.7 mL). The resulting reaction mixture was heated to and maintained at 85 °C for 2 h. The reaction was allowed to cool to rt and was then partitioned between EtOAc and saturated aqueous Na_2CO_3. The layers were separated and the aqueous layer was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried ($MgSO_4$), and adsorbed onto SiO_2. Purification by flash chromatography (2:1, 1:1, 1:2, 1:3 hexanes-EtOAc) provided 75 mg (0.25 mmol, 69 %) of an orange solid as **1d**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (br s, 1 H), 8.10 (d, J = 5.8 Hz, 1 H), 8.05 (br d, J = 4.4 Hz, 1 H), 7.95 (d, J = 2.8 Hz, 1 H), 7.76 (br d, J = 1.7 Hz 1 H), 7.30 (dd, J = 2.7, 9.1 Hz, 1 H), 6.91 (d, J = 9.3 Hz, 1 H), 6.60 (dd, J = 2.5, 5.8 Hz, 1 H), 3.05 (d, J = 5.2 Hz, 3 H), 2.16 (s, 3 H).

Step 4:



1d **1e**

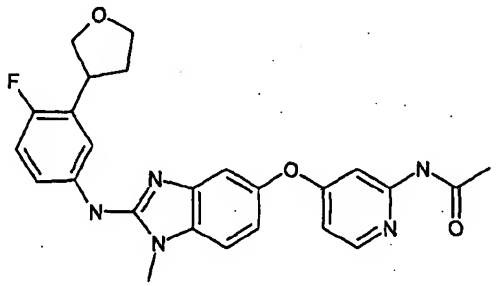
A suspension of acetamide **1d** (75 mg, 0.25 mmol) and 10% Pd/C (30 mg, 0.03 mmol) in methanol (5 mL) was charged with H_2 and the resulting reaction mixture was maintained under a H_2 atmosphere for 1 h at rt. The mixture was filtered and the

remaining solids washed thoroughly with EtOAc and methanol. The combined organic portions were evaporated to afford 60 mg (0.22 mmol, 88%) of a brown residue as the phenylene diamine, which was carried forward without further purification.

The above diamine (60 mg, 0.22 mmol) was dissolved in methanol (3 mL) and a solution of 3-*tert*-butyl phenylthioisocyanate (62 mg, 0.32mmol) in methanol was added. The reaction was maintained for 16 h. Pyridine (0.06 mL, 0.74 mmol) was added to the reaction, followed by ferric chloride (45 mg, 0.28 mmol). The resulting dark reaction mixture was maintained at rt for 16 h, then suspended in saturated aqueous Na_2CO_3 solution, and filtered with Celite. The remaining solids were washed with EtOAc and the combined filtrate was partitioned and separated. The aqueous portion was extracted with EtOAc (3 X) and the combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated. Purification by semi-prep HPLC gave **1e** as the TFA salt which was neutralized with saturated aqueous Na_2CO_3 solution and extracted with EtOAc (3 X). The combined organic portions were washed with brine and water, dried ($MgSO_4$), and evaporated. The resulting residue was reconstituted as the mono citrate salt: LCMS *m/z* 430.3 (MH^+), t_R = 2.24 min.

Example 2

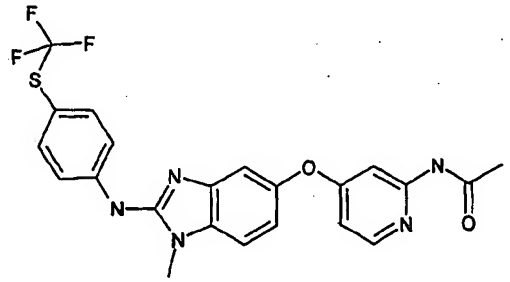
Synthesis of N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



Synthesized as described above in Example 1 using 3-(2-fluoro-5-isothiocyanato-phenyl)-tetrahydro-furan. LCMS *m/z* 462.2 (MH^+), R_t 2.51 min.

Example 3

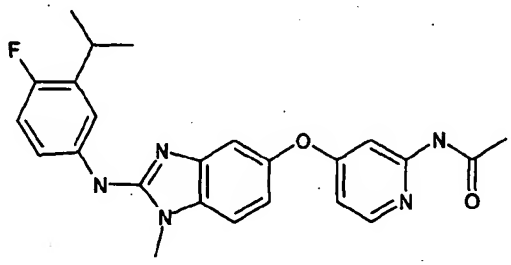
Synthesis of N-(4-{[1-methyl-2-({4-[(trifluoromethyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide



Synthesized as described above in Example 1 using 4-trifluoromethylthiophenyl isothiocyanate. LCMS *m/z* 474.2 (MH^+), R_t 3.41 min.

Example 4

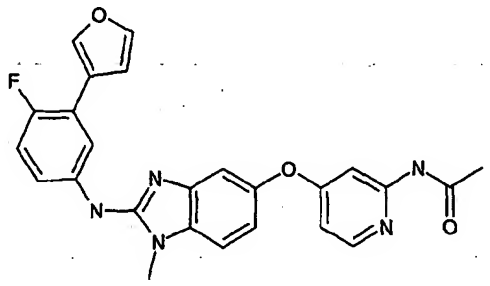
Synthesis of N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



Synthesized as described above in Example 1 using 4-fluoro-3-isopropylphenyl isothiocyanate. LCMS *m/z* 434.2 (MH^+), R_t 3.28 min.

Example 5

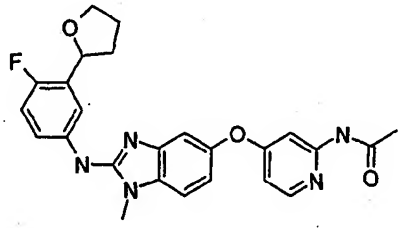
Synthesis of N-{4-[(2-{[4-fluoro-3-(3-furyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



Synthesized as described above in Example 1 using 3-(2-fluoro-5-isothiocyanato-phenyl)-furan. LCMS *m/z* 458.3 (MH^+), R_t 2.02 min.

Example 6

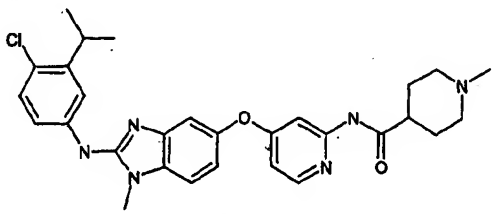
Synthesis of N-[4-({2-[(4-fluoro-3-tetrahydrofuran-2-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



Synthesized as described above in Example 1 using 2-(2-Fluoro-5-isothiocyanato-phenyl)-tetrahydro-furan. LCMS *m/z* 462.3 (MH^+), R_t 1.87 min.

Example 7

Synthesis of N-[4-({2-[(4-chloro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide



1. Synthesis of [(4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine

Bromine (1.3eq) was added dropwise to a solution of potassium hydroxide (10eq) at -10°C. 4-(4-methylamino-3-nitrophenoxy)-pyridine-2-carboxamide (1eq) was added followed by dioxane and the mixture was heated to 60°C for one hour. The mixture was then cooled to ambient temperature followed by slow addition of acetic acid (5eq). The solution was heated to 60°C for one hour. The solution was brought to pH=8 with acetic acid. [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine precipitated as an orange solid on cooling which was collected by filtration and washed with water and dried. MS: $MH^+ = 261$.

2. Synthesis of 1-methyl-*N*-(4-{[4-(methylamino)-3-nitrophenyl]oxy}pyridin-2-yl)-piperidine-4-carboxamide

To a mixture of 1-methylpiperidine-4-carboxylic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting 1-methyl-*N*-(4-{[4-(methylamino)-3-nitrophenyl]oxy}pyridin-2-yl)piperidine-4-carboxamide was purified by silica gel chromatography. MS: $MH^+ = 386.2$.

3. Synthesis of *N*-(4-{[3-amino-4-(methylamino)phenyl]oxy}pyridin-2-yl)-1-methylpiperidine-4-carboxamide

The mixture containing 1-methyl-*N*-(4-{[4-(methylamino)-3-nitrophenyl]oxy}-pyridin-2-yl)piperidine-4-carboxamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield *N*-(4-{[3-amino-4-(methylamino)phenyl]oxy}pyridin-2-yl)-1-methylpiperidine-4-carboxamide. MS: $MH^+ = 356.2$.

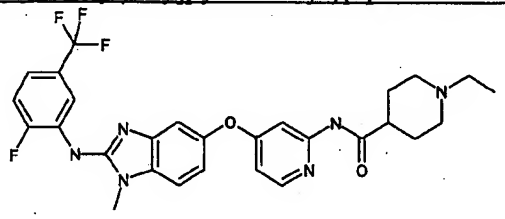
4. Synthesis of N-[4-({2-[(4-chloro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide

To 4-chloro-3-(methylethyl)benzeneisothiocyanate (1eq) in methanol was added *N*-(4-{[3-amino-4-(methylamino)phenyl]oxy}pyridin-2-yl)-1-methylpiperidine-4-carboxamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then

added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield N-N-[4-({2-[(4-chloro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide. MS: $MH^+ = 534.1$.

Example 8

Synthesis of 1-ethyl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide



1. Synthesis of 1-(ethyl)piperidine-4-carboxylic acid

To ethylpiperidine-4-carboxylate (1eq) in ethanol was added iodoethane (1.1eq) and potassium carbonate (2eq) and the resulting mixture was refluxed for 16h. The mixture was then cooled to room temperature and filtered. Ethanol was concentrated and partitioned between methylene chloride and water. The organic layer was then washed with saturated sodium chloride solution, dried with sodium sulfate and concentrated. To it was then added concentrated hydrochloric acid and water (2:1) and the mixture was refluxed for 5h. The resulting 1-(ethyl)piperidine-4-carboxylic acid was then azeotroped with toluene. MS: $MH^+ = 158$.

2. Synthesis of ((1-ethyl)(4-piperidyl))-N-{4-{4-(methylamino)-3-nitrophenoxy}(2-pyridyl)}carboxamide

To a mixture of 1-(ethyl)piperidine-4-carboxylic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting ((1-

ethyl)(4-piperidyl))-N-{4-[4-(methylamino)-3-nitrophenoxy]}(2-pyridyl))carboxamide was purified by silica gel chromatography. MS: MH^+ = 400.2.

3. Synthesis of N-[4-{3-amino-4-(methylamino)}phenoxy](2-pyridyl)-(1-ethyl(4-piperidyl))carboxamide

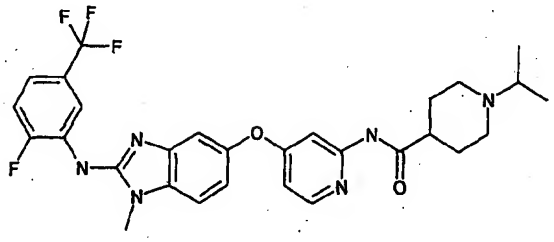
The mixture containing ((1-ethyl)(4-piperidyl))-N-{4-[4-(methylamino)-3-nitrophenoxy]}(2-pyridyl))carboxamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield N-[4-{3-amino-4-(methylamino)}phenoxy](2-pyridyl)-(1-ethyl(4-piperidyl))carboxamide. MS: MH^+ = 370.2.

4. Synthesis of 1-ethyl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-[4-{3-amino-4-(methylamino)}phenoxy](2-pyridyl)-(1-ethyl(4-piperidyl))-carboxamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To this in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield 1-ethyl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide. MS: MH^+ = 557.6.

Example 9

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide



1. Synthesis of 1-(methylethyl)piperidine-4-carboxylic acid

To ethylpiperidine-4-carboxylate (1eq) in methanol was added acetone (1eq) and acetic acid (5%) and the resulting mixture was stirred for 2h at ambient temperature. To it was then added sodium cyanoborohydride (1eq) and continued stirring for 16h. The mixture was then concentrated and to it was added sodium bicarbonate and was partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and concentrated to yield ethyl-1-(methylethyl)piperidine –4-carboxylate. To this was then added concentrated hydrochloric acid and water (2:1) and the mixture was refluxed for 5h. The resulting 1-(methylethyl)piperidine-4-carboxylic acid was then azeotroped with toluene. MS: $MH^+ = 172$.

2. Synthesis of N-{4-[4-(methylamino)3-nitrophenoxy](2-pyridyl)}-[1-(methylethyl)(4-piperidyl]carboxamide

To a mixture of 1-(methylethyl)piperidine-4-carboxylic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting N-{4-[4-(methylamino)3-nitrophenoxy](2-pyridyl)}-[1-(methylethyl)(4-piperidyl]carboxamide was purified by silica gel chromatography. MS: $MH^+ = 414.2$.

3. Synthesis of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-[1-methylethyl)(4-piperidyl)]carboxamide

The mixture containing N-{4-[4-(methylamino)3-nitrophenoxy](2-pyridyl)}-[1-(methylethyl)(4-piperidyl]carboxamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-[1-(methylethyl)(4-piperidyl)]carboxamide. MS: $MH^+ = 384.2$.

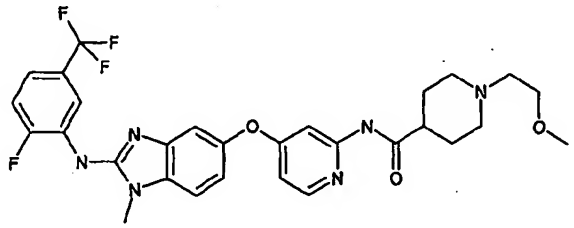
4. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-[1-(methylethyl)(4-piperidyl)]carboxamide (1eq) and the resulting mixture was stirred at ambient

temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide. MS: $MH^+ = 571.6$.

Example 10

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide



1. Synthesis of 1-(2-methoxyethyl)piperidine-4-carboxylic acid

To ethylpiperidine-4-carboxylate (1eq) in ethanol was added 2-bromo-1-methoxyethane (1eq) and potassium carbonate 2eq) and the resulting mixture was refluxed for 16h. The mixture was then filtered and concentrated. To it was then added ethanol and water (3:1) and sodium hydroxide (1eq) and it was refluxed for 16h. The resulting 1-(2-methoxyethyl)piperidine-4-carboxylic acid was then azeotroped with toluene. MS: $MH^+ = 188$.

2. Synthesis of [1-(2-methoxyethyl)(4-piperidyl)}-N-{4-[4-(methylamino)-3-nitrophenoxy](2-[pyridyl)}carboxamide

To a mixture of 1-(2-methoxyethyl)piperidine-4-carboxylic (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at

60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting [1-(2-methoxyethyl)(4-piperidyl)}-N-{4-[4-(methylamino)-3-nitrophenoxy](2-[pyridyl)}-carboxamide was purified by silica gel chromatography. MS: MH^+ = 430.2.

3. Synthesis of N-{4[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[1-(2-methoxyethyl)(4-piperidyl)]carboxamide

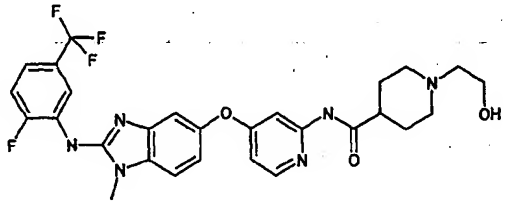
The mixture containing [1-(2-methoxyethyl)(4-piperidyl)}-N-{4-[4-(methyl-amino)-3-nitrophenoxy](2-[pyridyl)}carboxamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield N-{4[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[1-(2-methoxyethyl)(4-piperidyl)]carboxamide. MS: MH^+ = 400.2.

4. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-{4[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[1-(2-methoxyethyl)(4-piperidyl)]carboxamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through elite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide. MS: MH^+ = 587.6.

Example 11

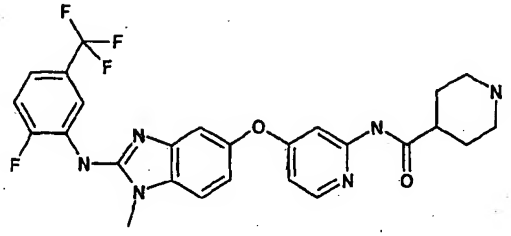
Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-hydroxyethyl)piperidine-4-carboxamide



To N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide (1eq) in methylene chloride at –78°C was added 1M borontribromide in methylene chloride (10eq) and the resulting mixture and the resulting mixture was stirred at –78°C for 1h. It was then brought to ambient temperature and stirred for 2h. LC/MS showed formation of the product. The reaction was quenched with saturated sodium carbonate solution at 0°C. The mixture was concentrated and then brought to pH=9. It was then extracted with ethyl acetate and the organic layer was dried with sodium sulfate and concentrated and purified on preparative chromatography to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-hydroxyethyl)-piperidine-4-carboxamide. MS: $MH^+ = 573.6$.

Example 12

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide



1. Synthesis of tert-butyl-4-(N-{4-[4-(methylamino)-3-nitrophenoxy]-2- pyridyl} carbamoyl)piperidinecarboxylate

To a mixture of 1-(tert-butoxy)carbonylpiperidine-4-carboxylic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting tert-butyl-4-(N-{4-[4-(methylamino)-3-nitrophenoxy]-2- pyridyl} carbamoyl) piperidinecarboxylate was purified by silica gel chromatography. MS: $MH^+ = 472.2$.

2. Synthesis of tert-butyl-4-(N-{4-[3-amino-4-(methylamino)phenoxy]-2-pyridyl-carbamoyl) piperidinecarboxylate

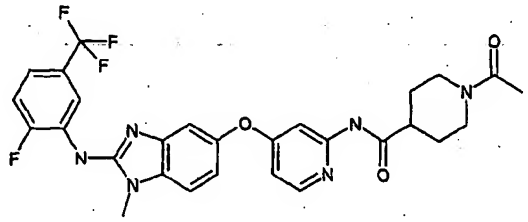
The mixture containing tert-butyl-4-(N-{4-[4-(methylamino)-3-nitrophenoxy]-2-pyridyl} carbamoyl) piperidinecarboxylate in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield tert-butyl-4-(N-{4-[3-amino-4-(methylamino)-phenoxy]-2-pyridylcarbamoyl) piperidinecarboxylate. MS: $MH^+ = 442.2$.

3. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added tert-butyl-4-(N-{4-[3-amino-4-(methylamino)phenoxy]-2-pyridylcarbamoyl) piperidinecarboxylate (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield the product. To it in methylene chloride was then added trifluoroacetic acid to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide. MS: $MH^+ = 529.5$.

Example 13

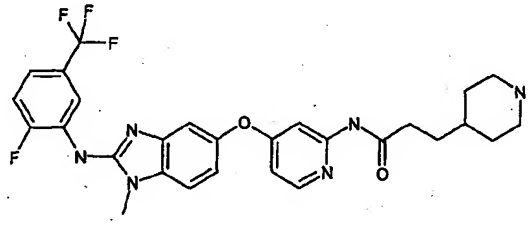
Synthesis of 1-acetyl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide



To N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide (1eq) in dioxane and N,N-disopropylethylamine (2eq) was added acetic anhydride (1eq) and the resulting mixture was stirred for 1h. 1-acetyl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide thus formed was purified by preparative chromatography. MS: $MH^+ = 571.5$.

Example 14

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-piperidin-4-ylpropanamide



1. Synthesis of tert-butyl-4-[2-(N-{4-{4-(methylamino)-3-nitrophenoxy]-2-pyridylcarbamoyl)ethyl] piperidinecarboxylate

To a mixture of 3-{1-[(tert-butyl)oxycarbonyl]-4-piperidyl}propanoic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned

between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting tert-butyl-4-[2-(N-{4-{4-(methylamino)-3-nitrophenoxy]-2-pyridylcarbamoyl)-ethyl] piperidinecarboxylate was purified by silica gel chromatography. MS: MH^+ = 500.2.

2. Synthesis of tert-butyl-4-[2-(N-{4-[3-amino-4-(methylamino)phenoxy]-2-pyridyl}carbamoyl)ethyl] piperidine carboxylate

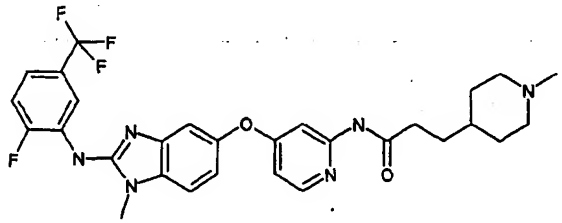
The mixture containing tert-butyl-4-[2-(N-{4-{4-(methylamino)-3-nitrophenoxy]-2-pyridylcarbamoyl)ethyl] piperidinecarboxylate in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield tert-butyl-4-[2-(N-{4-[3-amino-4-(methylamino)phenoxy]-2-pyridyl}carbamoyl)ethyl] piperidine carboxylate. MS: MH^+ = 470.2.

3. Synthesis of N-[4-(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino-1-methylbenz-imidazol-5-yloxy)(2-pyridyl]-3-(4-piperidyl)propanamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added tert-butyl-4-[2-(N-{4-[3-amino-4-(methylamino)phenoxy]-2-pyridyl}carbamoyl)-ethyl] piperidine carboxylate (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield the product. To it was then added trifluoroacetic acid to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-piperidin-4-ylpropanamide. MS: MH^+ = 557.6.

Example 15

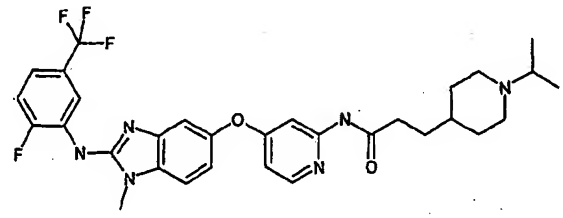
Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-(1-methylpiperidin-4-yl)propanamide



To N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-piperidin-4-ylpropanamide (1eq) in methanol was added formalin (2eq) and acetic acid(5%) followed by sodium cyanoborohydride (2eq) and the resulting mixture was stirred at ambient temperature for 3h. LC/MS showed formation of the product. The crude mixture was then concentrated and to it was added sodium bicarbonate and the resulting mixture was partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and purified by preparative chromatography to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-(1-methylpiperidin-4-yl)propanamide. MS: $MH^+ = 571.6$.

Example 16

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-(1-isopropylpiperidin-4-yl)propanamide

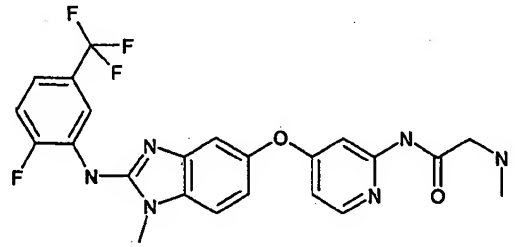


1. Synthesis of N-[4-(2-{[2-fluoro-5-trifluoromethyl)phenyl]amino)-1-methylbenzimidazol-5-yloxy)(2-pyridyl)]-3-[1-(methylethyl)(4-piperidyl)]propanamide

To N-[4-(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino-1-methylbenzimidazol-5-yloxy)(2-pyridyl]-3-(4-piperidyl)propanamide (1eq) in methanol was added acetone (2eq) and acetic acid(5%) followed by sodium cyanoborohydride (2eq) and the resulting mixture was stirred at ambient temperature for 3h. LC/MS shows formation of the product. The crude mixture was then concentrated and to it was added sodium bicarbonate and the resulting mixture was partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and purified by preparative chromatography to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-(1-isopropylpiperidin-4-yl)propanamide. MS: $MH^+ = 599.6$.

Example 17

Synthesis of N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~-methylglycinamide



1. Synthesis of 2-[(tert-butoxy)-N-methylcarbonylamino]-N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)acetamide

To a mixture of 2-[(tert-butoxy)-N-methylcarbonylamino]acetic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting 2-[(tert-butoxy)-N-methylcarbonylamino]-N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)acetamide was purified by silica gel chromatography. MS: $MH^+ = 432.2$.

2. Synthesis of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[(tert-butoxy)-N-methylcarbonylamino]acetamide

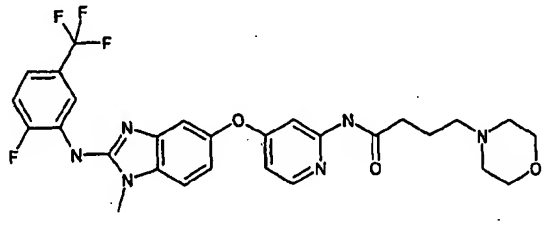
The mixture containing 2-[(tert-butoxy)-N-methylcarbonylamino]-N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)acetamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[(tert-butoxy)-N-methylcarbonylamino]acetamide. MS: MH^+ = 402.2.

3. Synthesis of N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~-methylglycinamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[(tert-butoxy)-N-methyl-carbonylamino]acetamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield the product. To it in methylene chloride was then added trifluoroacetic acid to yield N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~-methylglycinamide. MS: MH^+ = 489.4.

Example 18

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-4-morpholin-4-ylbutanamide



1. Synthesis of N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}-4-morpholino-4-ylbutanamide

To a mixture of 4-morpholino-4-ylbutanoic acid (1eq) in N,N-dimethyl formamide and N,N-disopropylethylamine (4eq) was added BOP (2eq) and the mixture was stirred at ambient temperature until homogeneous. To it was added [4-(2-amino(4-pyridyloxy))-2-nitrophenyl]methylamine (1eq) and the resulting mixture was stirred at 60°C for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}-4-morpholino-4-ylbutanamide was purified by silica gel chromatography. MS: $MH^+ = 416.2$.

2. Synthesis of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl))-4-morpholin-4-ylbutanamide

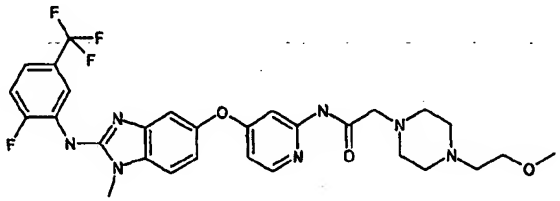
The mixture containing N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}-4-morpholino-4-ylbutanamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl))-4-morpholin-4-ylbutanamide. MS: $MH^+ = 386.2$.

3. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-4-morpholin-4-ylbutanamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl))-4-morpholin-4-ylbutanamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-4-morpholin-4-ylbutanamide. MS: $MH^+ = 573.6$.

Example 19

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide



1. Synthesis of 2-[4-(2-methoxyethyl)piperizinyl]-N-{4-[4-(methylamino-3-nitrophenoxy](2-pyridyl)}acetamide

To 2-chloro-N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}acetamide (1eq) in acetonitrile was added 1-methoxy-2-piperizinylethane (1eq) and potassium carbonate (2eq) and the resulting mixture was heated to 60°C for 16h. It was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium sulfate and concentrated to give 2-[4-(2-methoxyethyl)piperizinyl]-N-{4-[4-(methyl-amino-3-nitrophenoxy](2-pyridyl)}acetamide. MS: MH^+ = 445.2.

2. Synthesis of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[4-(2-methoxyethyl) piperizinyl]acetamide

The mixture containing 2-[4-(2-methoxyethyl)piperizinyl]-N-{4-[4-(methyl-amino-3-nitrophenoxy](2-pyridyl)}acetamide in methanol with catalytic amount of Lindlar's catalyst was hydrogenated to yield N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[4-(2-methoxyethyl)piperizinyl]acetamide. MS: MH^+ = 415.2.

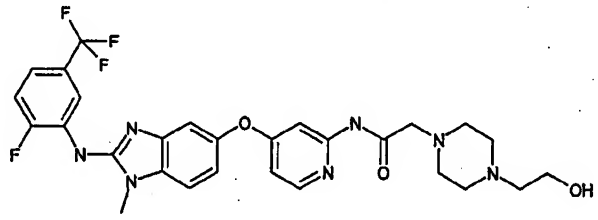
3. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide

To 2-fluoro-5-(trifluoromethyl)benzeneisothiocyanate (1eq) in methanol was added N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-[4-(2-methoxyethyl)-piperizinyl]acetamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of the corresponding thiourea. To it in methanol was then added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to basic pH with saturated sodium

carbonate solution. The aqueous solution was filtered through celite and was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude was then triturated with hot ether with a few drops of ethyl acetate to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide. MS: $MH^+ = 602.6$.

Example 20

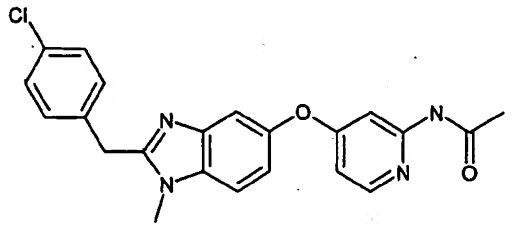
Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-hydroxyethyl)piperazin-1-yl]acetamide



To N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide (1eq) in methylene chloride at –78°C was added 1M borontribromide in methylene chloride (10eq) and the resulting mixture was stirred at –78°C for 1h. It was then brought to ambient temperature and stirred for 2h. LC/MS showed formation of the product. The reaction was quenched with saturated sodium carbonate solution at 0°C. The mixture was concentrated and then brought to pH=9. It was then extracted with ethyl acetate and the organic layer was dried with sodium sulfate and concentrated and purified on preparative chromatography to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-hydroxyethyl)piperazin-1-yl]-acetamide. MS: $MH^+ = 588.6$.

Example 21

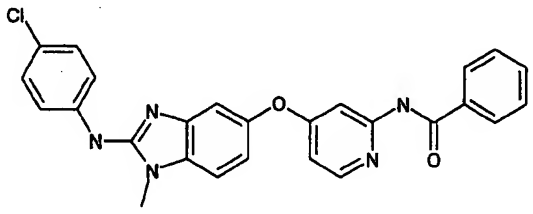
Synthesis of N-(4-{[2-(4-chlorobenzyl)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide



To N-{4-[3-amino-4-(methylamino)phenoxy]}-2-pyridylacetamide (1eq) in tetrahydrofuran added EDC (2eq) and HOAT (1eq) and N,N-disopropylethylamine (4eq) and 2-(4-chlorophenyl)acetic acid (1eq) and the resulting mixture was stirred at ambient temperature for 16h. The reaction mixture was then partitioned between ethyl acetate and water. The organic layer was then dried with sodium sulfate and concentrated to give N-{4-[2-(acetylamino)(4-pyridyloxy)]-2-aminophenyl}-2-(4-chlorophenyl)-N-methyl-acetamide. To it was added acetic acid and the resulting mixture was heated to 60°C for 4h. The crude was purified by preparative chromatography to give N-(4-{[2-(4-chlorobenzyl)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide. MS: MH^+ = 407.9.

Example 22

Synthesis of N-[4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]benzamide

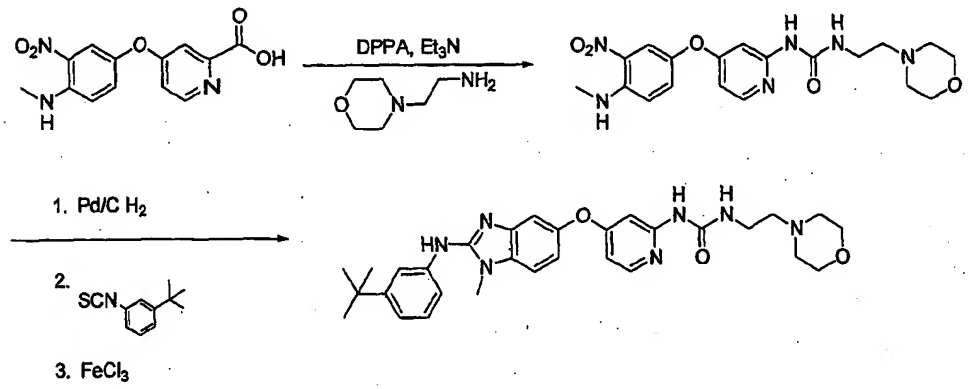


To [5-(2-amino(4-pyridyloxy))-1-methylbenzimidazol-2-yl](4-chlorophenyl)-amine (1eq) in tetrahydrofuran added EDC (2eq) and HOAT (1eq) and N,N-disopropylethylamine (4eq) and benzoic acid (1eq) and the resulting mixture was stirred at ambient temperature for 16h. The reaction mixture was then partitioned between ethyl

acetate and water. The organic layer was then dried with sodium sulfate and concentrated and purified by preparative chromatography to to give N-[4-({2-[(4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]benzamide. MS: MH^+ = 470.9.

Example 23

Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N'-(2-morpholin-4-ylethyl)urea



Step 1: Synthesis of N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}[(2-morpholin-4-ylethyl)amino]carboxamide

A flame dried flask was charged with 4-[4-(methylamino)-3-nitrophenoxy]-pyridine-2-carboxylic acid (1eq), diphenylphosphoryl azide (1.1eq), triethylamine (2.1eq) and 20 ml toluene and heated for one and one half hours at 75°C. To this was added 2-morpholin-4-ylethylamine (1.2eq) and the resulting mixture was stirred at 75°C overnight. The reaction was then concentrated and partitioned between ethyl acetate and distilled water. The organic layer was dried with sodium sulfate and concentrated and titurated with ether then hexanes to give the purified product. MS: MH^+ = 417.

Step 2: Synthesis of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[(2-morpholin-4-ylethyl)amino]carboxamide

To a flask containing N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}[(2-morpholin-4-ylethyl)amino]carboxamide in methanol was added a catalytic amount of 10% Pd/C and hydrogenated to yield in quantitative amount N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[(2-morpholin-4-ylethyl)amino]carboxamide.MS: MH^+ = 387.

Step 3: Synthesis of 3-(tert-butyl)benzenisothiocyanate

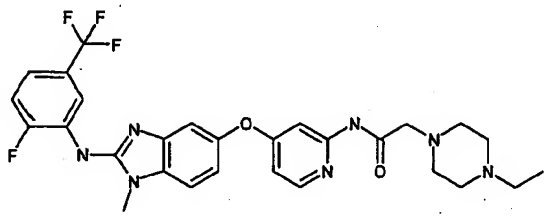
To 3-(tert-butyl)phenylamine in acetone at 0°C was added sodium bicarbonate (2eq) and thiophosgene (2eq). The mixture was brought to ambient temperature and concentrated and partitioned between ethyl acetate and water. The organic layer was dried with sodium bicarbonate and sodium sulfate and concentrated to yield 3-(tert-butyl)benzenisothiocyanate. MS: $MH^+ = 192$.

Step 4: Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N'-(2-morpholin-4-ylethyl)urea

To 3-(tert-butyl)benzenisothiocyanate (1eq) in methanol was added N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}[(2-morpholin-4-ylethyl)amino]carboxamide (1eq) and the resulting mixture was stirred at ambient temperature for 16h. LC/MS showed formation of corresponding thiourea. To this was added anhydrous ferric chloride (1.5eq) and stirred for 3h. The reaction mixture was then concentrated to half its volume and brought to neutral pH with 1N sodium hydroxide. It was then extracted with ethyl acetate and the organic layer was washed with brine and dried with sodium sulfate. The crude material was then purified on preparative chromatography to yield N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N'-(2-morpholin-4-ylethyl)urea. MS: $MH^+ = 544$.

Example 24

Synthesis of 2-(4-ethylpiperazin-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



1. Synthesis of N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-chloroacetamide

A solution of 4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-amine (1eq) and triethylamine (2 eq) in tetrahydrofuran was treated with 2-chloroacetyl chloride and

stirred for 15 minutes at room temperature. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with brine, dried over sodium sulfate and concentrated in vacuum to give crude product. Purification on silica gel with 2% methanol in methylene chloride gave N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-chloroacetamide as a bright orange solid. HPLC = 3.82min; MS: $MH^+ = 337$.

2. Synthesis of N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide

The mixture containing N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-chloroacetamide (1eq), 1-ethylpiperazine (3eq), and potassium carbonate (4eq) was stirred in dimethylformamide at 60°C for 1 hour. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was separated and washed with water then brine, dried over sodium sulfate and concentrated to give orange solid. Purification on silica gel with 20% methanol in methylene chloride gave N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-(4-ethylpiperazin-1-yl)-acetamide as a red solid. HPLC = 3.26min; MS: $MH^+ = 415$.

3. Synthesis of N-(4-(3-amino-4-(methylamino)phenoxy)pyridin-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide

The mixture containing N-(4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide in methanol with a catalytic amount of 10% Pd/C poisoned with lead was hydrogenated until the disappearance of the yellow color. The reaction was then filtered to remove the catalyst and concentrated to yield N-(4-(3-amino-4-(methylamino)phenoxy)pyridin-2-yl)-2-(4-ethylpiperazin-1-yl)acetamide as a brown oil. HPLC = 2.00 min; MS: $MH^+ = 385$.

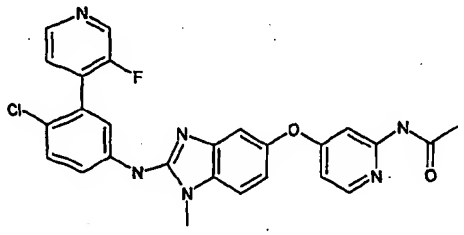
4. Synthesis of 2-(4-ethylpiperazin-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]-amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide

A solution of N-(4-(3-amino-4-(methylamino)phenoxy)pyridin-2-yl)-2-(4-ethyl-piperazin-1-yl)acetamide (1eq) in methanol was treated with 1-fluoro-4-(trifluoromethyl)-2-isothiocyanatobenzene (1eq) and stirred at room temperature for 16 hours to form the corresponding thiourea. To it was then added iron (III) chloride (1.2eq) and stirred for another 4 hours. The mixture was then concentrated and partitioned between saturated

sodium carbonate and ethyl acetate. The organic layer was separated and washed with water and brine, dried over sodium sulfate and concentrated to give brown crude solid. Purification by trituration with 5% ethyl acetate in diethyl ether to give 2-(4-ethylpiperazin-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide as tan solid. HPLC = 3.40min; MS: $MH^+ = 572$.

Example 25

Synthesis of N-{4-[(2-{[4-chloro-3-(3-fluoropyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



1. Synthesis of 4-(2-chloro-5-nitrophenyl)-3-fluoropyridine

A mixture of DME: H2O (3:1) was degassed with N_2 for one half hour. 2-bromo-1-chloro-4-nitrobenzene (1eq) added and degassed for another 10 minutes. 1,1'-bis(diphenylphosphino)ferrocene palladium(II)chloride (0.05eq), 3-fluoropyridin-4-yl-4-boronic acid (1eq), and sodium carbonate (3eq) were then added and stirred at 100°C for 16 hours. Reaction then concentrated and partitioned between ethyl acetate and water. Organic layer washed with brine, dried over sodium sulfate and concentrated. Purification on silica gel, 10% ethyl acetate in hexanes to yield 4-(2-chloro-5-nitrophenyl)-3-fluoropyridine. HPLC = 4.57min; MS: $MH^+ = 253$.

2. Synthesis of 4-chloro-3-(3-fluoropyridin-4-yl)benzenamine

4-(2-chloro-5-nitrophenyl)-3-fluoropyridine (1eq) was stirred with Iron (0), (3eq), in acetic acid for 10 hours at room temperature. Reaction neutralized with sodium carbonate and filtered to remove iron. Reaction partitioned between ethyl acetate and water. Organic layer separated and washed with brine, dried over sodium sulfate and concentrated to give 4-chloro-3-(3-fluoropyridin-4-yl)benzenamine. HPLC = 1.72min; MS: $MH^+ = 223$.

3. Synthesis of 4-(2-chloro-5-isothiocyanatophenyl)-3-fluoropyridine

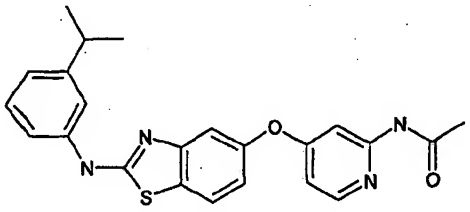
The mixture containing 4-chloro-3-(3-fluoropyridin-4-yl)benzenamine (1eq) and sodium bicarbonate (2eq) in acetone was treated with thiophosgene (2eq) and stirred for 5 minutes at 0°C. Reaction then concentrated and partitioned between ethyl acetate and water. Organic layer dried over sodium sulfate and sodium bicarbonate and concentrated to give 4-(2-chloro-5-isothiocyanatophenyl)-3-fluoropyridine. HPLC = 5.54min; MS: $MH^+ = 265$.

4. Synthesis of N-{4-[(2-{[4-chloro-3-(3-fluoropyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide

The mixture containing 4-(2-chloro-5-isothiocyanatophenyl)-3-fluoropyridine (1eq) and N-(4-(3-amino-4-(methylamino)phenoxy)pyridin-2-yl)acetamide (1eq) in methanol was stirred at room temperature of 16 hours to give the corresponding thiourea. To it was then added iron (III) chloride (1.2eq) and stirred for another 4 hours. The mixture was then concentrated and partitioned between saturated sodium carbonate and ethyl acetate. The organic layer was separated and washed with water and brine, dried over sodium sulfate and concentrated to give brown crude solid. Purification on HPLC to yield N-{4-[(2-{[4-chloro-3-(3-fluoropyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide. HPLC = 3.37min; MS: $MH^+ = 503$

Example 26

Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]acetamide



1. Synthesis of N-(3-isopropylphenyl)-5-methoxybenzo[d]thiazol-2-amine

The mixture containing 2-bromo-5-methoxybenzo[d]thiazole (1eq), 3-isopropylbnezylamine (1.5eq) and diisopropylethylamine (4eq) was subjected to microwave in NMP at 235°C for 15 minutes. Reaction partitioned between ethyl acetate

and water. Organic layer separated and washed with brine, dried over sodium sulfate and concentrated. Purification on silica gel, 10% ethyl acetate in hexane to give N-(3-isopropylphenyl)-5-methoxybenzo[d]thiazol-2-amine. HPLC = 5.50min; MS: MH^+ = 299.

2. Synthesis of 2-(3-isopropylphenylamino)benzo[d]thiazol-5-ol

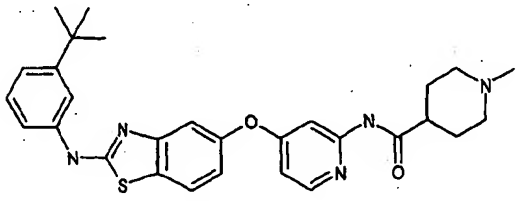
N-(3-isopropylphenyl)-5-methoxybenzo[d]thiazol-2-amine was charged with hydrobromic acid (45%) and subjected to microwave at 170°C for 10 minutes. Reaction was then neutralized with sodium carbonate (saturated solution) and partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to give 2-(3-isopropylphenylamino)benzo[d]thiazol-5-ol. HPLC = 4.63min; MS: MH^+ = 285.

3. Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]acetamide

The mixture containing 2-(3-isopropylphenylamino)benzo[d]thiazol-5-ol (1eq), N-(4-chloropyridin-2-yl)acetamide (1.4eq), potassium bis(trimethylsilyl)amide (4eq) and potassium carbonate (1.2eq) in dimethylformamide was subjected to the microwave at 200°C for 15 minutes. The reaction was then partitioned between ethyl acetate and water. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to give the crude product. Purification on HPLC to yield N-[4-({2-[(3-isopropylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]acetamide. HPLC = 4.87min; MS: MH^+ = 419.

Example 27

Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide



1. Synthesis of 1-methylpiperidine-4-carbonyl chloride

A flask was flame dried and placed under a nitrogen atmosphere. 1-methylpiperidine-4-carboxylic acid (1eq) in anhydrous methylene chloride added to flask and cooled to 20°C in a water bath. Dimethylformamide added, then oxalyl chloride (1.4eq) in methylene chloride. Reaction refluxed for 2 hours, brought to room temperature, concentrated and azeotroped with toluene to yield 1-methylpiperidine-4-carbonyl chloride as a light yellow fluffy solid. MS: $MH^+ = 162$.

2. Synthesis of N-(4-chloropyridin-2-yl)-1-methylpiperidine-4-carboxamide

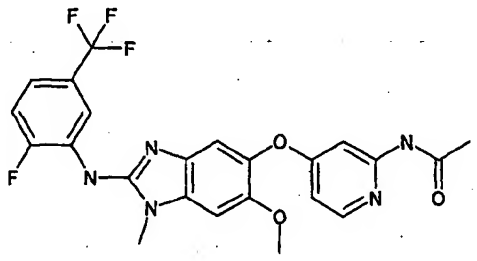
A flask was flame dried and placed under a nitrogen atmosphere. 1-methylpiperidine-4-carbonyl chloride (1eq) in anhydrous methylene chloride was added to the flask and brought to 0°C. To this was added the solution containing 4-chloropyridin-2-amine (1eq), and diisopropylethylamine (5eq) in anhydrous methylene chloride, which was stirred for 1 hour at 0°C. Reaction concentrated and partitioned between water and ethyl acetate. The organic layer was separated, washed with brine, dried over sodium sulfate and concentrated to give the crude product. Purification on silica gel, 10% methanol in methylene chloride to yield N-(4-chloropyridin-2-yl)-1-methylpiperidine-4-carboxamide as a slightly yellow crystal solid. HPLC = 2.39min; MS: $MH^+ = 254$.

3. Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide

The mixture containing 2-(3-tert-butylphenylamino)benzo[d]thiazol-5-ol (1eq), potassium bis(trimethylsilyl)amide (4eq), and potassium carbonate (1.2eq) in dimethylformamide was stirred at room temperature for 10 minutes. N-(4-chloropyridin-2-yl)-1-methylpiperidine-4-carboxamide (1.4eq) was then added and mixture subjected to microwave at 220°C for 20 minutes. Reaction partitioned between ethyl acetate and water. Organic layer separated, washed with brine, dried over sodium sulfate and concentrated to give crude product. Purification by HPLC to yield N-[4-({2-[(3-tert-butylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide. HPLC = 4.74min; MS: $MH^+ = 516$.

Example 28

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-6-methoxy-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



1. Synthesis of 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxylic acid

Trifluoroacetic acid was added neat to tert-butyl 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxylate and stirred at room temperature for 5 hours. TFA was evaporated, solid product azeotroped with toluene then placed under vacuum for 24 hours to yield 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxylic acid. HPLC = 3.07min; MS: $MH^+ = 321$

2. Synthesis of 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxamide

The mixture containing 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxylic acid (1eq), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (2eq), 3H-1,2,3-triazolo[4,5-b]pyridine-3-ol (1.5eq), and diisopropylamine (5eq) in tetrahydrofuran was stirred at room temperature for 1hour. To this was then added ammonium chloride (2eq) and the resulting mixture was stirred together for 48 hours. Reaction concentrated. Purification on silica gel, 50% acetone in hexanes to yield 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxamide as a bright yellow solid. HPLC = 3.70min; MS: $MH^+ = 319$.

3. Synthesis of 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridin-2-amine

Liquid bromine (2eq) was added dropwise to a solution of potassium hydroxide (10eq) in water at 0°C. 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridine-2-carboxamide (1eq) was then added in a small amount of dioxane. Reaction brought to room temperature for ½ hour then heated to 55°C for 1 hour showing a red homogenous

solution. The reaction was brought back to 0°C and acetic acid (excess) was added. The mixture was heated at 55°C for ½ hour, cooled to room temperature and sodium carbonate added to neutralize. Reaction was extracted with methylene chloride. Organic layer washed with brine, dried over sodium sulfate and concentrated to yield 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridin-2-amine as an orange solid. HPLC = 3.10min; MS: $MH^+ = 292$.

4. Synthesis of N-(4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridin-2-yl)acetamide

Under a nitrogen atmosphere, 4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)-pyridin-2-amine (1eq) and diisopropylethylamine (4eq) in methylene chloride was brought to 0°C. Acetyl chloride (1.1eq) was added dropwise and mixture stirred for 5 minutes. Reaction brought to room temperature and water added. Organic layer washed with brine, dried over sodium sulfate and concentrated to yield N-(4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)pyridin-2-yl)acetamide. HPLC = 3.21min; MS: $MH^+ = 333$.

5. Synthesis of N-(4-(5-amino-2-methoxy-4-(methylamino)phenoxy)pyridin-2-yl)acetamide

The mixture containing N-(4-(2-methoxy-4-(methylamino)-5-nitrophenoxy)-pyridin-2-yl)acetamide in methanol with a catalytic amount of 10% Pd/C poisoned with lead was hydrogenated until the disappearance of the yellow color. The reaction was then filtered to remove the catalyst and concentrated to yield N-(4-(5-amino-2-methoxy-4-(methylamino)phenoxy)pyridin-2-yl)acetamide. HPLC = 2.25min; MS: $MH^+ = 303$.

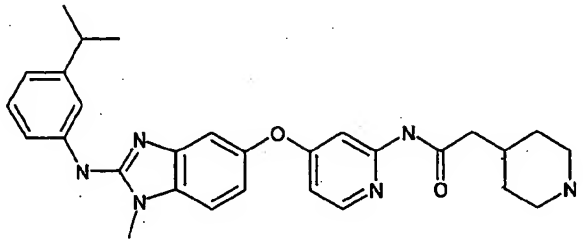
6. Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-6-methoxy-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide

A solution of N-(4-(5-amino-2-methoxy-4-(methylamino)phenoxy)pyridin-2-yl)acetamide (1eq) in methanol was treated with 1-fluoro-4-(trifluoromethyl)-2-isothiocyanatobenzene (1eq) and stirred at room temperature for 16 hours to form the corresponding thiourea. To it was then added iron (III) chloride (1.2eq) and stirred for another 4 hours. The mixture was then concentrated and partitioned between saturated sodium carbonate and ethyl acetate. The organic layer was separated and washed with water and brine, dried over sodium sulfate and concentrated to give brown crude solid.

Purification by HPLC to yield N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-6-methoxy-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide HPLC = 3.02min; MS: $MH^+ = 490$.

Example 29

Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-4-ylacetamide



1. Synthesis of 5-(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo[d]imidazol-2-amine

The mixture containing 4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-amine (1eq) and 1-isopropyl-3-isothiocyanatobenzene (1eq) in methanol was stirred at room temperature for 16 hours to form the corresponding thiourea. To it was then added iron (III) chloride (1.2eq) and stirred for another 4 hours. The mixture was then concentrated and partitioned between saturated sodium carbonate and ethyl acetate. The organic layer was separated and washed with water and brine, dried over sodium sulfate and concentrated to give brown crude solid. Purification by trituration with toluene to give 5-(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo[d]imidazol-2-amine as brown solid. HPLC = 3.63min; MS: $MH^+ = 374$.

2. Synthesis of tert-butyl 4-((4-(2-(3-isopropylphenylamino)-1-methyl-1H-benzo[d]imidazol-5-yloxy)pyridin-2-ylcarbamoyl)methyl)piperidine-1-carboxylate

To a mixture of 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (1eq) in N,N-dimethyl formamide and N,N,disopropylethylamine (4eq) was added HATU (2eq) and the mixture was stirred at ambient temperature until it becomes homogeneous. To it was added 5-(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo-[d]imidazol-2-amine (1eq) and 4-(dimethylamino)pyridine (0.05eq) and the resulting

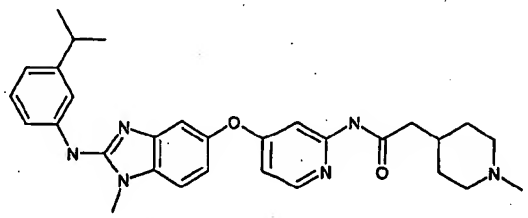
mixture was stirred at room temperature for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting tert-butyl 4-((4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-ylcarbamoyl)methyl)piperidine-1-carboxylate was purified by HPLC. HPLC = 4.63min; MS: $MH^+ = 599$.

3. Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-4-ylacetamide

To tert-butyl 4-((4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-ylcarbamoyl)-methyl)piperidine-1-carboxylate (1eq) in water and acetonitrile was added trifluoroacetic acid (2eq) and stirred at room temperature for 16 hours. The resulting solution was frozen with liquid nitrogen and the lyophilized sample yielded N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-4-ylacetamide. HPLC = 3.49min; MS: $MH^+ = 499$.

Example 30

Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(1-methylpiperidin-4-yl)acetamide



1. Synthesis of 5-(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo[d]imidazol-2-amine

The mixture containing 4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-amine (1eq) and 1-isopropyl-3-isothiocyanatobenzene (1eq) in methanol was stirred at room temperature for 16 hours to form the corresponding thiourea. To it was then added iron (III) chloride (1.2eq) and stirred for another 4 hours. The mixture was then concentrated and partitioned between saturated sodium carbonate and ethyl acetate. The organic layer was separated and washed with water and brine, dried over sodium sulfate and concentrated to give brown crude solid. Purification by trituration with toluene to give 5-

(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo[d]imidazol-2-amine as brown solid. HPLC = 3.63min; MS: $MH^+ = 374$.

2. Synthesis of tert-butyl 4-((4-(2-(3-isopropylphenylamino)-1-methyl-1H-benzo[d]imidazol-5-yloxy)pyridin-2-ylcarbamoyl)methyl)piperidine-1-carboxylate

To a mixture of 2-(1-(tert-butoxycarbonyl)piperidin-4-yl)acetic acid (1eq) in N,N-dimethyl formamide and N,N,disopropylethylamine (4eq) was added HATU (2eq) and the mixture was stirred at ambient temperature until it becomes homogeneous. To it was added 5-(2-aminopyridin-4-yloxy)-N-(3-isopropylphenyl)-1-methyl-1H-benzo[d]-imidazol-2-amine (1eq) and 4-(dimethylamino)pyridine (0.05eq) and the resulting mixture was stirred at room temperature for 16h. The reaction mixture was then concentrated and partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate and the resulting tert-butyl 4-((4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-ylcarbamoyl)methyl)piperidine-1-carboxylate was purified by HPLC. HPLC = 4.63min; MS: $MH^+ = 599$.

3. Synthesis of N-(4-(2-(3-isopropylphenylamino)-1-methyl-1H-benzo[d]imidazol-5-yloxy)pyridin-2-yl)-2-(piperidin-4-yl)acetamide

To tert-butyl 4-((4-(4-(methylamino)-3-nitrophenoxy)pyridin-2-ylcarbamoyl)-methyl)piperidine-1-carboxylate (1eq) in water and acetonitrile was added trifluoroacetic acid (2eq) and stirred at room temperature for 16 hours. The resulting solution was frozen with liquid nitrogen and the lyophilized sample yielded N-(4-(2-(3-isopropylphenylamino)-1-methyl-1H-benzo[d]imidazol-5-yloxy)pyridin-2-yl)-2-(piperidin-4-yl)acetamide. HPLC = 3.49min; MS: $MH^+ = 499$.

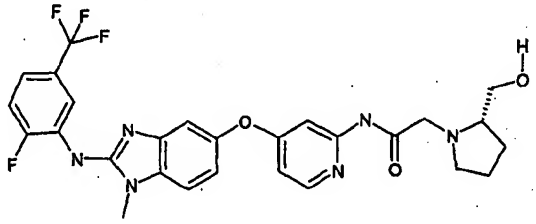
4. Synthesis of N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(1-methylpiperidin-4-yl)acetamide

To the mixture containing N-(4-(2-(3-isopropylphenylamino)-1-methyl-1H-benzo[d]imidazol-5-yloxy)pyridin-2-yl)-2-(piperidin-4-yl)acetamide (1eq), glacial acetic acid (2 eq), and formaline (7.5eq) in tetrahydrofuran:methanol (1:1) was added sodium cyanoborohydride (2eq) and stirred at room temperature for one hour. Reaction neutralized with saturated sodium carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate and concentrated to

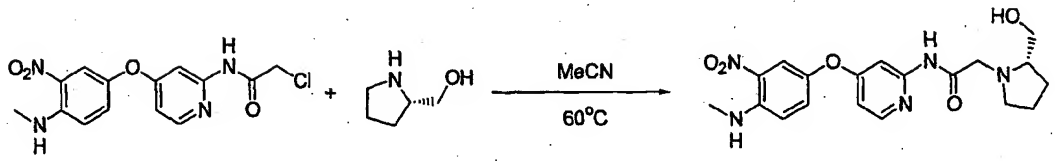
give crude product. Purification by HPLC to yield N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(1-methylpiperidin-4-yl)acetamide. HPLC = 3.51min; MS: MH^+ = 513.

Example 31

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]acetamide

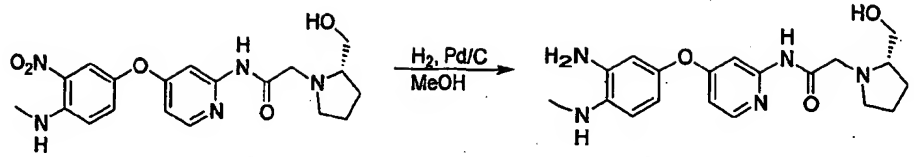


Step 1:



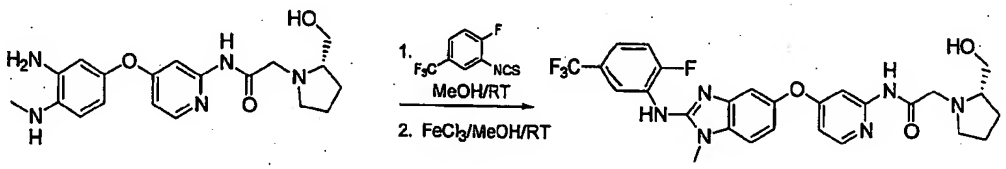
L-Prolinol (3.0 eq) was added to a mixture of 2-chloro-N-{4-[4-(methylamino)-2-nitrophenoxy](2-pyridyl)}acetamide (1 eq) in acetonitrile. The resulting mixture was brought to 60°C. LC/MS showed quantitative conversion after stirring for 1 hour. The reaction was concentrated to about half the volume of solvent and then partitioned between water and ethyl acetate. The aqueous layer was extracted 2x with ethyl acetate. The organic layers were combined and washed with water followed by saturated sodium chloride, dried over magnesium sulfate and concentrate to yield pure product. MS: MH^+= 402.2.

Step 2:



2-(2-Hydroxymethyl-pyrrolidin-1-yl)-N-[4-(4-methylamino-3-nitro-phenoxy)-pyridin-2-yl]-acetamide was hydrogenated in methanol in the presence of Pd/C for 4 hours. The catalyst was removed via filtration through Celite and filtrate was concentrated to give N-[4-(3-Amino-4-methylamino-phenoxy)-pyridin-2-yl]-2-(2-hydroxymethyl-pyrrolidin-1-yl)-acetamide. MS: MH^+= 372.4.

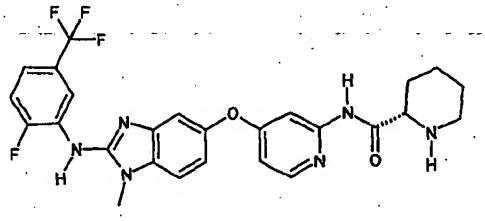
Step 3:



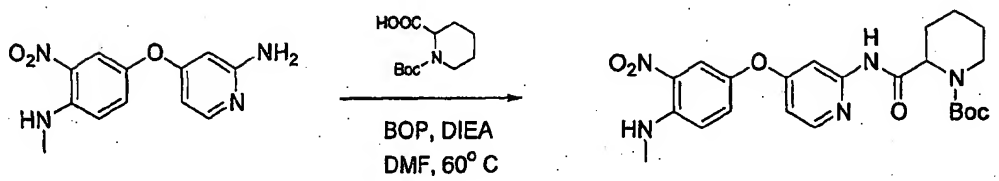
2-Fluoro-5-(trifluoromethyl)phenyl isothiocyanate was added to a solution of N-[4-(3-Amino-4-methylamino-phenoxy)-pyridin-2-yl]-2-(2-hydroxymethyl-pyrrolidin-1-yl)-acetamide in methanol. Reaction was stirred at room temperature for 15 hours. Thiourea formation was confirmed by LC/MS. Ferric chloride was added and the resulting mixture was stirred at room temperature for 4 hours. After cyclization was complete by LC/MS the reaction mixture was concentrated and aqueous sodium carbonate was added until basic pH. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water then brine, and dried over magnesium sulfate and concentrated. The crude product was purified by reverse phase HPLC. MS: MH^+= 559.3.

Example 32

Synthesis of (2S)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-2-carboxamide

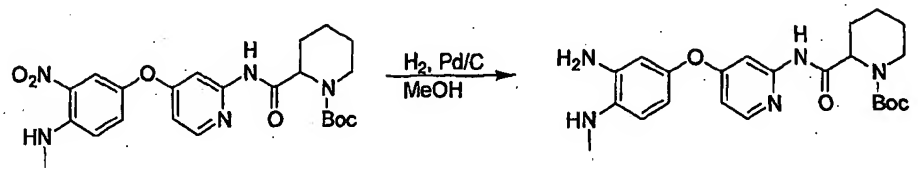


Step 1:



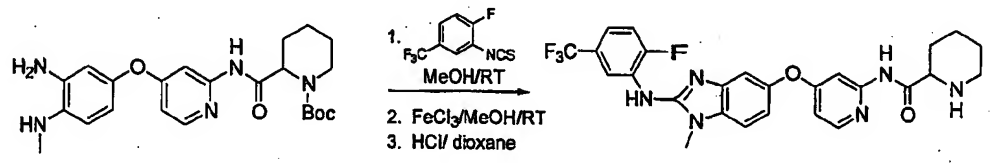
N-Boc homoproline (1.0 eq) was added to a solution of the amino pyridine (1.0 eq), BOP (2.0 eq) and diisopropylethylamine (3.0 eq) in DMF. The solution is heated overnight at 60°C. The solution is concentrated on a rotovap to about one fourth its original volume, then poured into water and EtOAc. The layers are separated and the organic is washed with water and then brine, dried over $MgSO_4$, filtered, silica added, and the solution is concentrated. The product is then purified by column chromatography (gradient of 2% MeOH: DCM -> 10% MeOH: DCM) to yield the desired product MH+ = 472.5.

Step 2:



The nitroaniline was hydrogenated in methanol in the presence of Pd/C for 4 hours. The catalyst was removed via filtration through Celite and filtrate was concentrated to give phenylenediamine. MS: MH^+= 442.4.

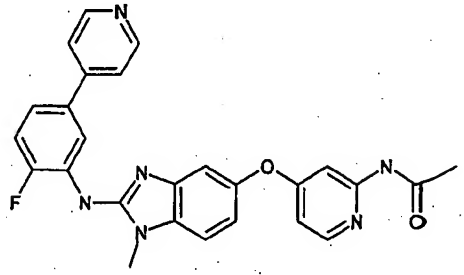
Step 3:



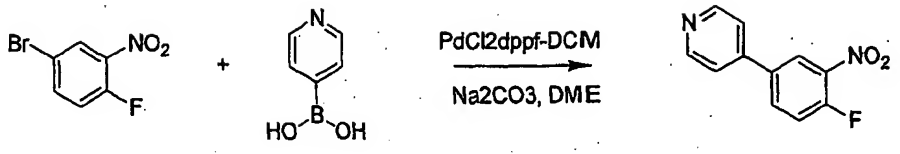
2-Fluoro-5-(trifluoromethyl)phenyl isothiocyanate was added to a solution of phenylenediamine in methanol. Reaction was stirred at room temperature for 15 hours. Thiourea formation was confirmed by LC/MS. Ferric chloride was added and the resulting mixture was stirred at room temperature for 4 hours. After cyclization was complete by LC/MS the reaction mixture was concentrated and aqueous sodium carbonate was added until basic pH. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water then brine, and dried over sodium sulfate and concentrated. The protecting group is removed by treating the crude product with HCl in dioxane for 30 minutes at room temperature whereupon the solvent is removed. The crude product was purified by reverse phase HPLC. MS: MH^+= 529.5.

Example 33

Synthesis of N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide

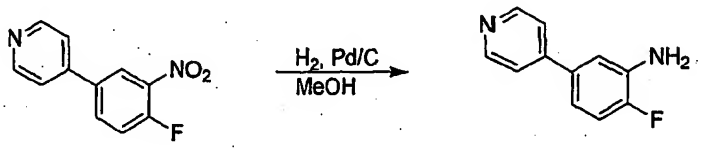


Step 1:



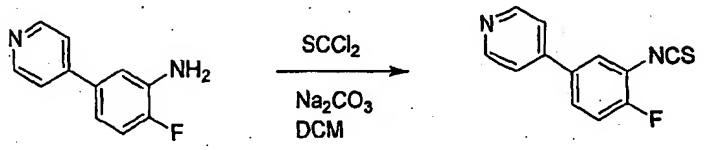
5-Bromo-2-fluoronitrobenzene (1.0 eq), 4-pyridylboronic acid (2.0 eq), and [1,1'-bis(diphenylphosphino)ferocene] dichloro palladium (II) complex with DCM are mixed in ethyleneglycol dimethylether and 2M aqueous sodium carbonate (4.0 eq). The solution is purged with argon for 20 minutes and then heated overnight at 100°C. At this time the reation mixture is cooled and then poured into water and EtOAc. The layers are separated and the organic is washed with water and then brine, dried over $MgSO_4$, filtered, silica added, and the solution is concentrated. The product is then purified by column chromatography (gradient of 1% MeOH: DCM -> 10% MeOH: DCM) to yield the desired product. MS: MH^+= 219.2.

Step 2:



The nitrophenyl compound was hydrogenated in methanol in the presence of Pd/C for 4 hours. The catalyst was removed via filtration through Celite and filtrate was concentrated to give the desired aniline. MS: MH^+= 189.2.

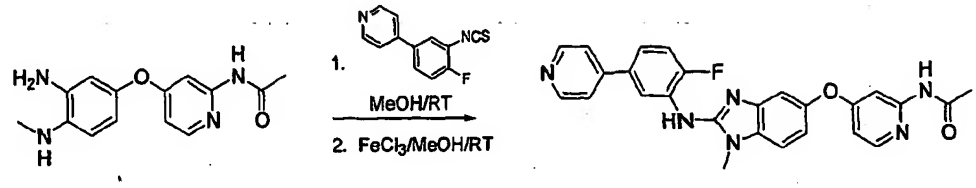
Step 3:



The aniline (1.0 eq) was cooled in a biphasic mixture of dichloromethane and sodium carbonate (4.0 eq) to 0° C. At this time thiophosgene (1.0 eq) was added. The

solution was allowed to stir for 30 minutes at which time the phases were separated and the organic phase was dried over magnesium sulfate.

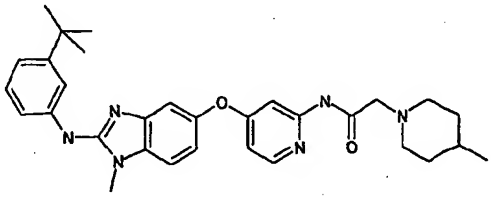
Step 4:



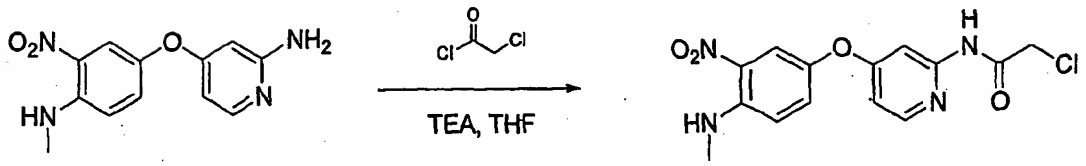
2-fluoro-5-(4-pyridyl)phenyl isothiocyanate was added as a solution in dcm to a solution of phenylenediamine in methanol. Reaction was stirred at room temperature for 15 hours. Thiourea formation was confirmed by lc/ms. Ferric chloride was added and the resulting mixture was stirred at room temperature for 4 hours. After cyclization was complete by lc/ms the reaction mixture was concentrated and aqueous sodium carbonate was added until basic ph. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water then brine, and dried over magnesium sulfate and concentrated. The crude product was purified by reverse phase HPLC. MS: MH+= 469.5.

Example 34

Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperidin-1-yl)acetamide

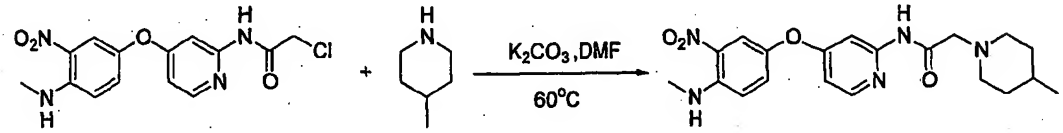


Step 1:



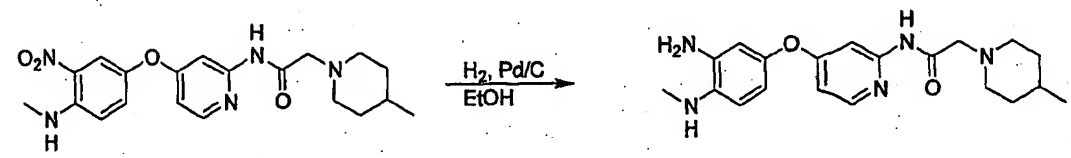
Chloroacetyl chloride (1.4 eq) was added dropwise over 15 minutes to a stirring solution of the amino pyridine (1.0 eql) and triethylamine (2.7 eq) in THF (1.2 L) at room temperature. After 2 hours LC shows 80% conversion to the desired product with a small amount of starting material and some bis acylated product (<10%) as well. The solution is concentrated on a rotovap to about one fourth its original volume, then poured into water and EtOAc. The layers are separated and the organic is washed with water and then brine, dried over $MgSO_4$, filtered, silica added, and the solution is concentrated. The product is then purified by column chromatography (gradient of 30% EtOAc: hexanes -> 60% EtOAc hexanes) to yield the desired product (39% yield).

Step 2:



4-Methylpiperidine (2.8 eq) was added to a mixture of 2-chloro-N-{4-[4-(methylamino)-2-nitrophenoxy](2-pyridyl)}acetamide (1 eq), and potassium carbonate (3.3 eq) in dimethylformamide. The resulting mixture was brought to 60°C. LC/MS showed quantitative conversion after stirring for 1 hour. The reaction was partitioned between water and ethyl acetate. The aqueous layer was extracted 2x with ethyl acetate. The organic layers were combined and washed with water followed by saturated sodium chloride, dried over sodium sulfate and concentrated. The crude product was passed through a plug of silica and eluted with 10% methanol/ methylene chloride. MS: MH^+= 400.2.

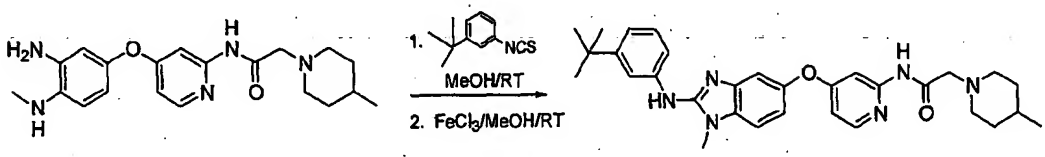
Step 3:



N-{4-[4-(methylamino)-3-nitrophenoxy](2-pyridyl)}-2-(4-methylpiperidyl)acetamide was hydrogenated in the presence of Pd/C for 4 hours. The catalyst was removed

via filtration and filtrate was concentrated to give N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-(4-methylpiperidyl)acetamide. MS: MH^+= 370.2.

Step 4:



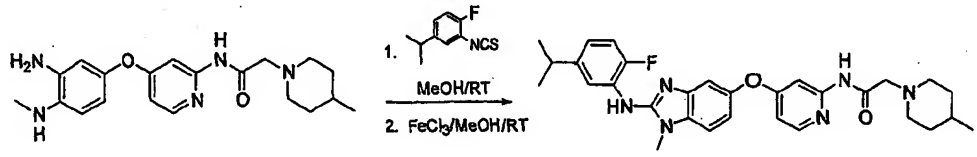
3-(tert-Butyl)benzenisothiocyanate was added to a solution of N-{4-[3-amino-4-(methylamino)phenoxy](2-pyridyl)}-2-(4-methylpiperidyl)acetamide in methanol. Reaction was stirred at room temperature for 15 hours. Thiourea formation was confirmed by LC/MS. Ferric chloride was added and the resulting mixture was stirred at room temperature for 4 hours. After cyclization was complete by LC/MS the reaction mixture was concentrated and aqueous sodium carbonate was added until basic pH. The reaction mixture was partitioned between ethyl acetate and water. The organic layer was washed with water then brine, and dried over sodium sulfate and concentrated. The crude product was purified by reverse phase HPLC. MS: MH+= 527.2.

Examples 35-68

The gylcinamides in Examples 35-68 were synthesized in a manner similar to that described above using the indicated starting materials and reagents.

Example 35

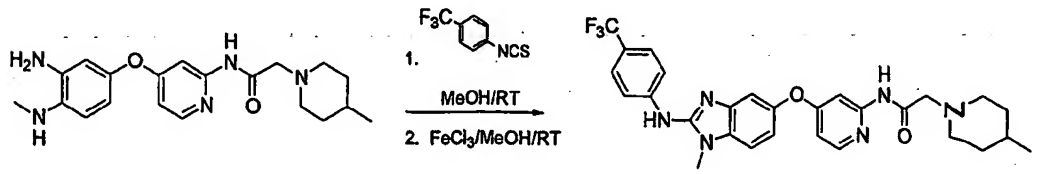
Synthesis of N-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperidin-1-yl)acetamide



MS: MH^+= 531.1.

Example 36

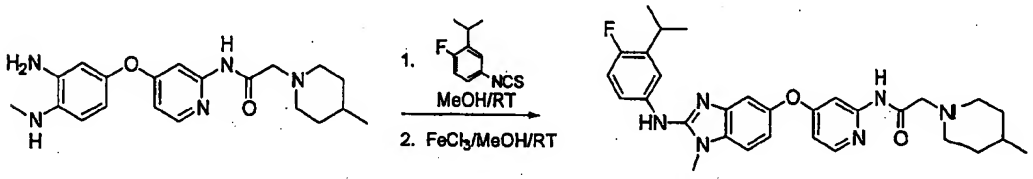
Synthesis of 2-(4-methylpiperidin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



MS: MH^+= 539.1.

Example 37

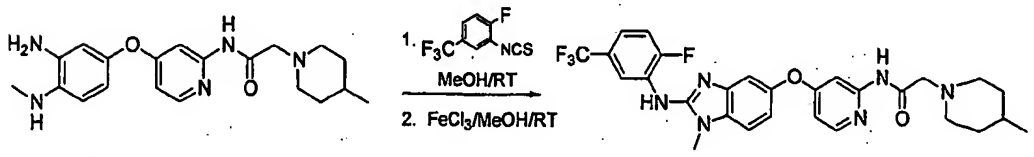
Synthesis of N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperidin-1-yl)acetamide



MS: MH^+= 531.1.

Example 38

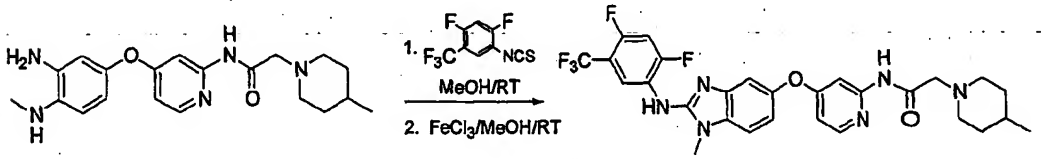
Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methylpiperidin-1-yl)acetamide



MS: MH^+= 557.1.

Example 39

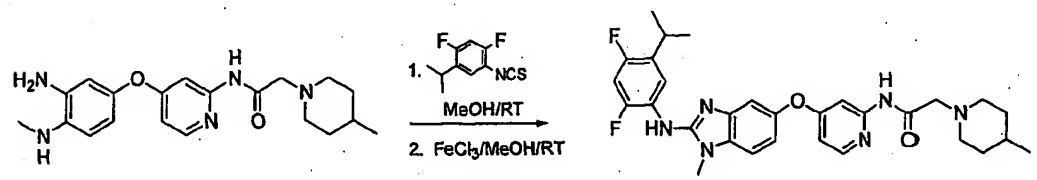
Synthesis of N-{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methylpiperidin-1-yl)acetamide



MS: MH^+= 575.0.

Example 40

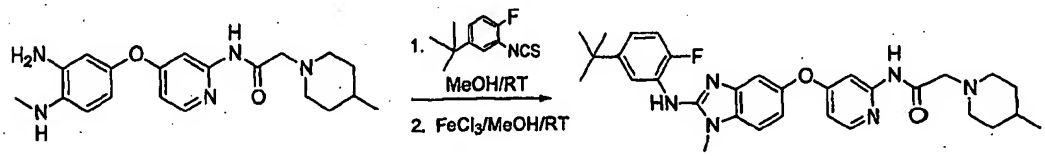
Synthesis of N-[4-({2-[(2,4-difluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperidin-1-yl)acetamide



MS: MH^+= 549.1.

Example 41

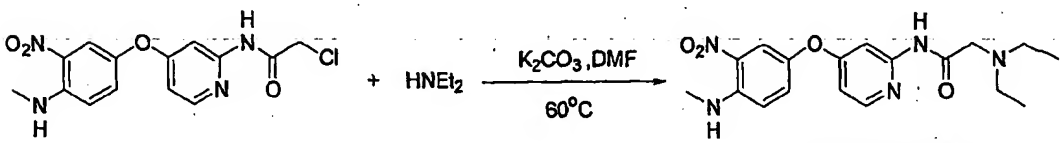
Synthesis of N-[4-({2-[(5-tert-butyl-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperidin-1-yl)acetamide

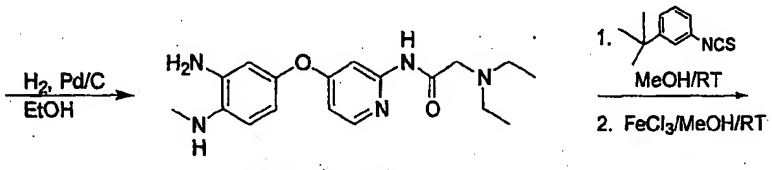


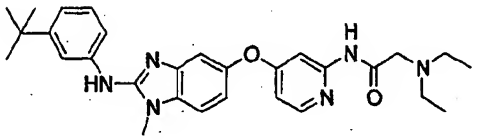
MS: MH^+= 545.1.

Example 42

Synthesis of N~1~~[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~~diethylglycinamide

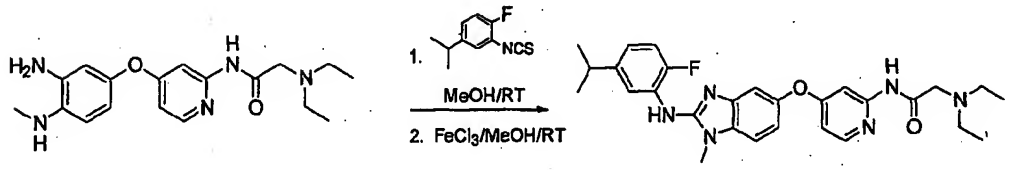






Example 43

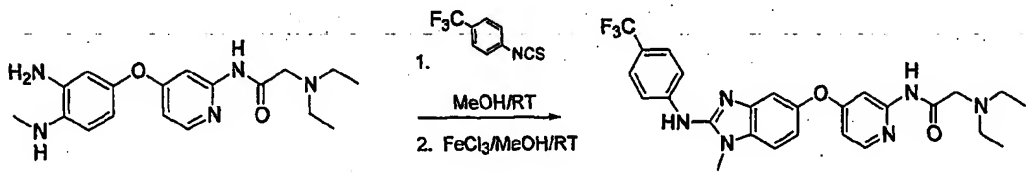
Synthesis of N~2~,N~2~~diethyl-N~1~~[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide



MS: MH^+= 505.1.

Example 44

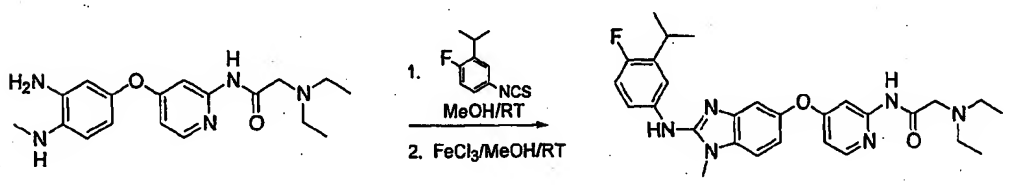
Synthesis of N~2~,N~2~-diethyl-N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide



MS: MH^+= 513.0.

Example 45

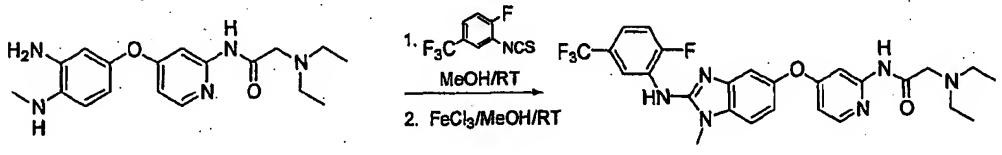
Synthesis of N~2~,N~2~-diethyl-N~1~-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide



MS: MH^+= 505.1.

Example 46

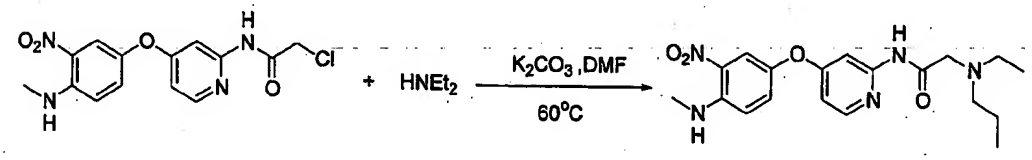
Synthesis of N~2~,N~2~-diethyl-N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide



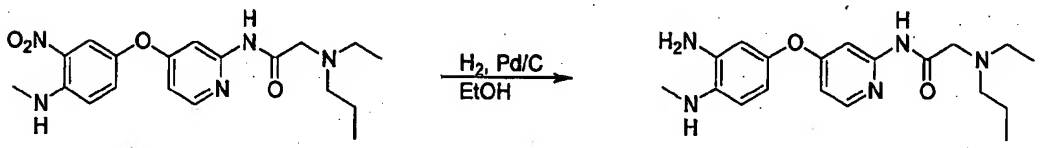
MS: MH^+= 531.1.

Example 47

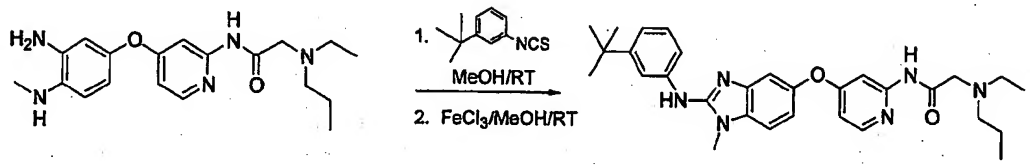
Synthesis of N~1~-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-ethyl-N~2~-propylglycinamide



MS: MH^+= 388.3.



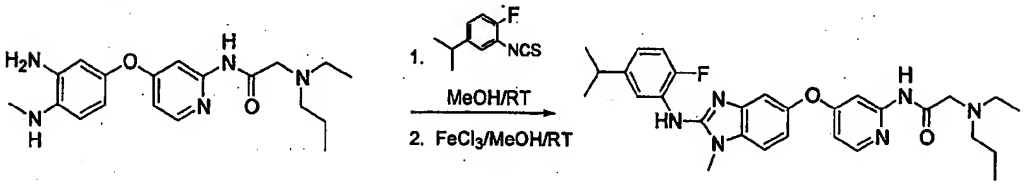
MS: MH^+= 358.2.



MS: MH^+= 515.1.

Example 48

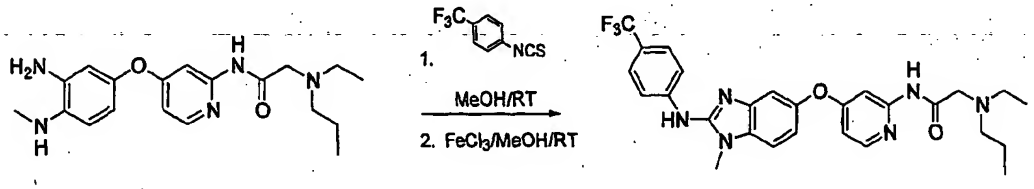
Synthesis of N~2~-ethyl-N~1~-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-propylglycinamide



MS: MH^+= 519.1.

Example 49

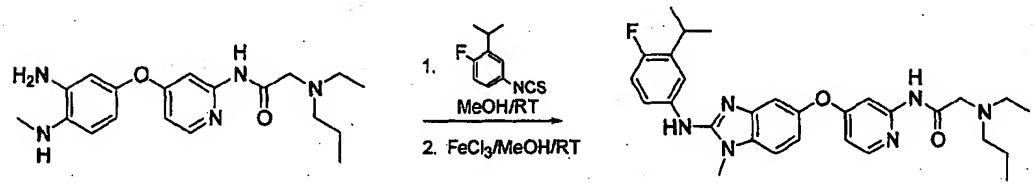
Synthesis of N~2~~ethyl-N~1~~{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~~propylglycinamide



MS: MH^+= 527.1.

Example 50

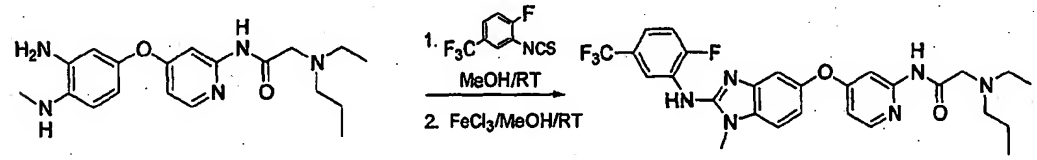
Synthesis of N~2~~ethyl-N~1~~[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~~propylglycinamide



MS: MH^+= 519.1.

Example 51

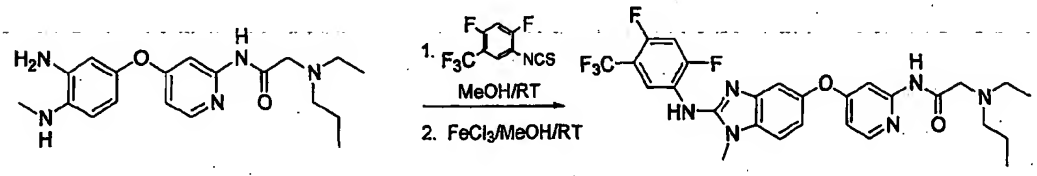
Synthesis of N~2~~ethyl-N~1~~{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~~propylglycinamide



MS: MH^+= 545.1.

Example 52

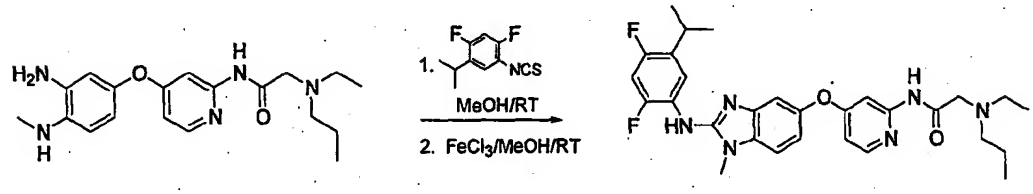
Synthesis of N~1~~{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~~ethyl-N~2~~propylglycinamide



MS: MH^+= 563.0.

Example 53

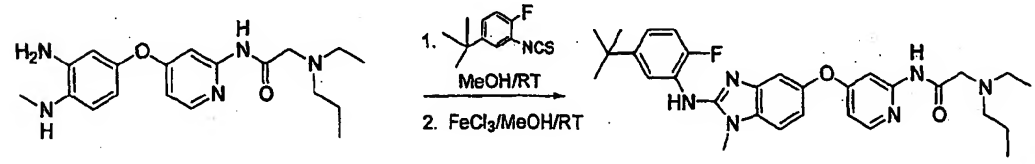
Synthesis of N~1~~[4-({2-[(2,4-difluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~~ethyl-N~2~~propylglycinamide



MS: MH^+= 537.1.

Example 54

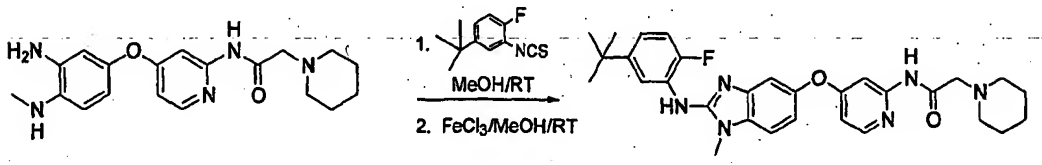
Synthesis of N~1~~[4-({2-[(5-tert-butyl-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~~ethyl-N~2~~propylglycinamide



MS: MH^+= 533.1.

Example 55

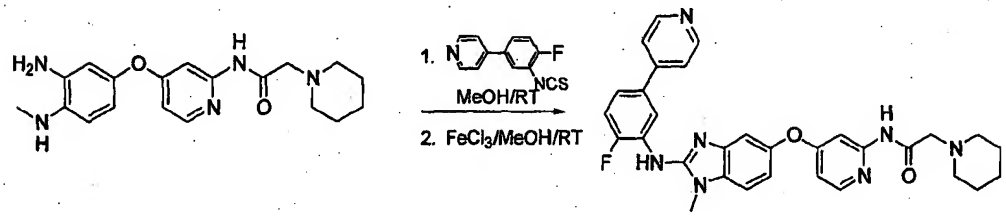
Synthesis of N-[4-({2-[(5-tert-butyl-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide



MS: MH^+= 531.2.

Example 56

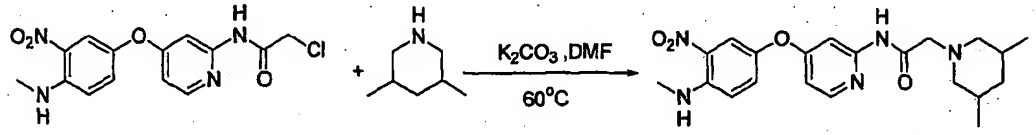
Synthesis of N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide



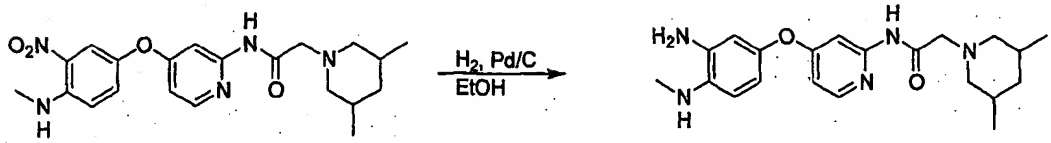
MS: MH^+= 552.1.

Example 57

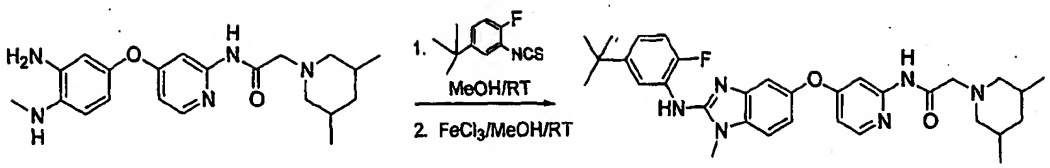
Synthesis of N-[4-({2-[(5-tert-butyl-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3,5-dimethylpiperidin-1-yl)acetamide



MS: MH^+= 414.1.



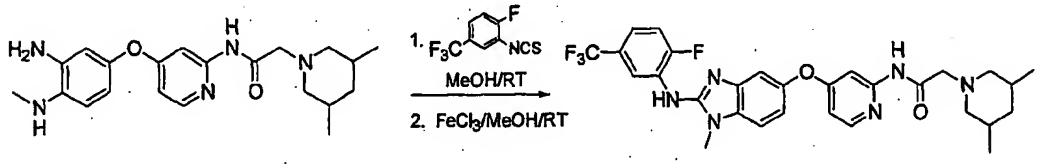
MS: MH^+= 384.2



MS: MH^+= 559.2.

Example 58

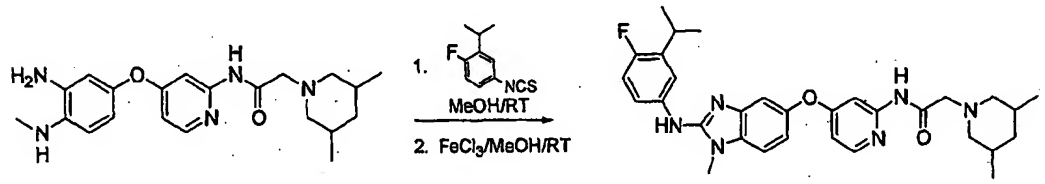
Synthesis of 2-(3,5-dimethylpiperidin-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



MS: MH^+= 571.1

Example 59

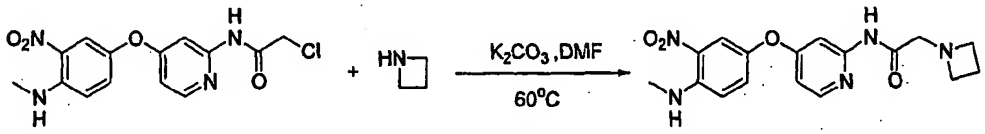
Synthesis of 2-(3,5-dimethylpiperidin-1-yl)-N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



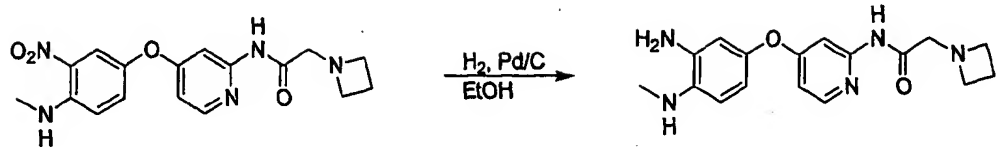
MS: MH^+= 545.2.

Example 60

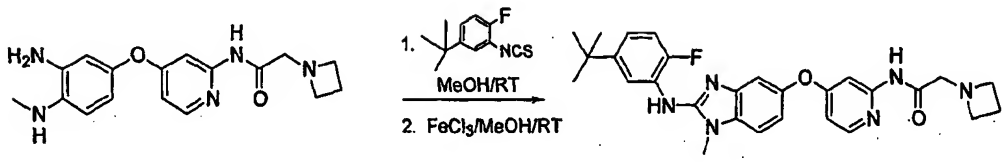
Synthesis of 2-azetidin-1-yl-N-[4-({2-[(5-tert-butyl-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



MS: MH^+= 358.1.



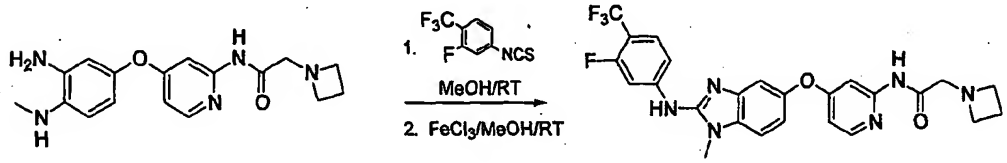
MS: MH^+= 328.1.



MS: MH^+= 503.1.

Example 61

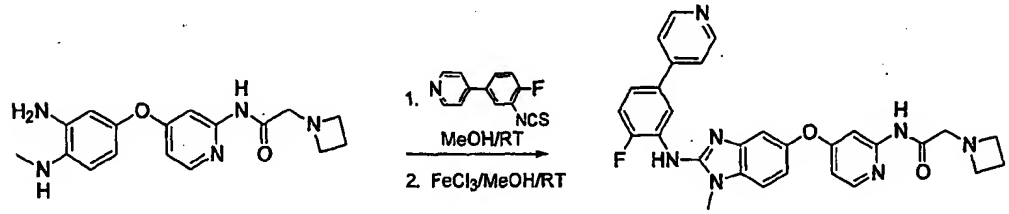
Synthesis of 2-azetidin-1-yl-N-{4-[(2-{[3-fluoro-4-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



MS: MH^+= 515.0.

Example 62

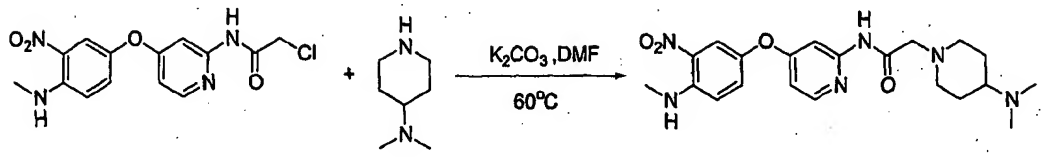
Synthesis of 2-azetidin-1-yl-N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



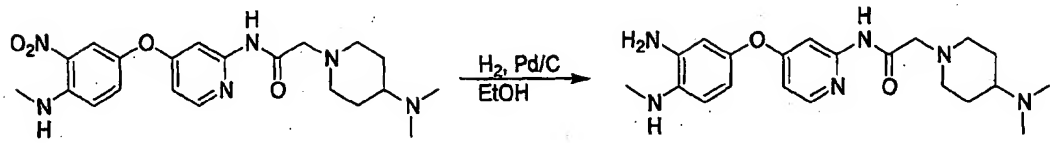
MS: MH^+= 524.1.

Example 63

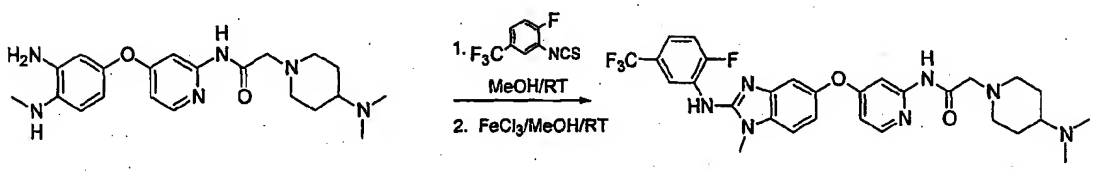
Synthesis of 2-[4-(dimethylamino)piperidin-1-yl]-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



MS: MH^+= 429.1.



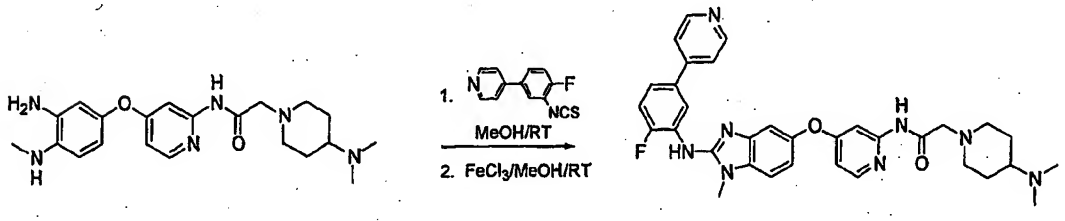
MS: MH^+= 399.2.



MS: MH^+= 586.1.

Example 64

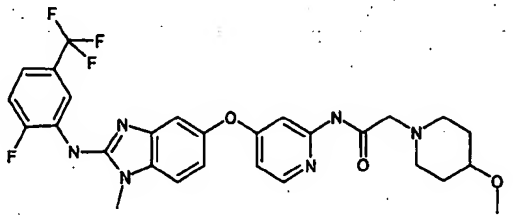
Synthesis of 2-[4-(dimethylamino)piperidin-1-yl]-N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide



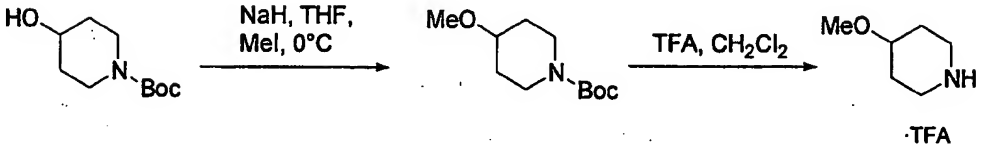
MS: MH^+= 595.2.

Example 65

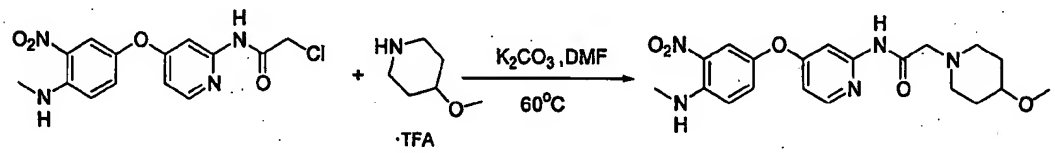
Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methoxypiperidin-1-yl)acetamide



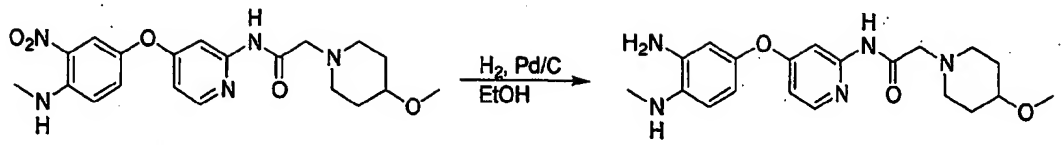
Step 1:



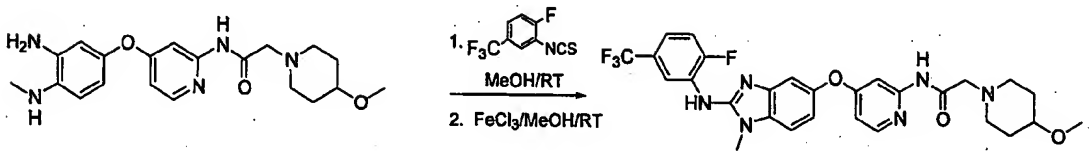
1-N-Boc-4-hydroxypiperidine (1.0 eq; O.Takuna, H. Yoshitaka, Y. Kaoru, O. Yoshitaka, M. Hideaki. WO2003018019. Preparation of Substituted 2-(1,1-Dioxaperhydro-1,4-thiazepin-7-yl)acetamides for Treating Inflammatory Respiratory Disease) in THF (10 mL) was added to NaH (2.7 eq) in THF (20 mL) at 0°C. After 20 min, MeI (1.1 eq) was added dropwise. This mixture stirred for 2 h and was then quenched with H_2O and extracted twice with EtOAc. The organic layer was dried over sodium sulfate and concentrated. MS: MH^+= 216.1 (MH^+-*t*-Bu). The material was dissolved in CH_2Cl_2 and TFA (3:1) and stirred overnight. The solvent was then removed by rotory evaporation to give a clear oil. MS: MH^+= 116.0.



MS: MH^+= 416.1.



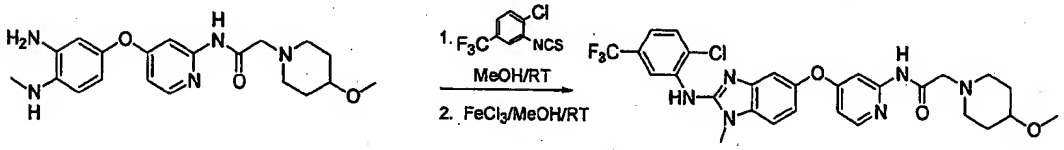
MS: MH^+= 386.2.



MS: MH^+= 573.1.

Example 66

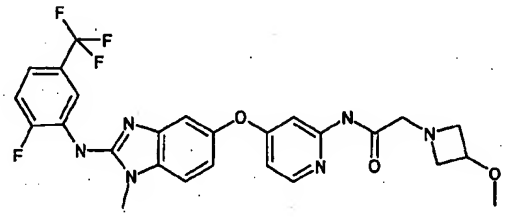
Synthesis of N-{4-[(2-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methoxypiperidin-1-yl)acetamide

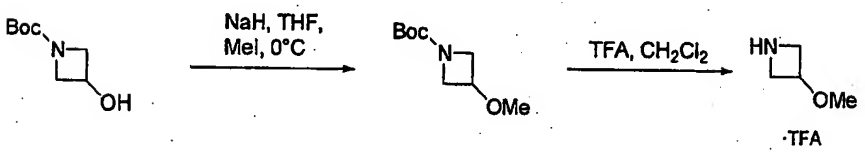


MS: MH^+= 589.1.

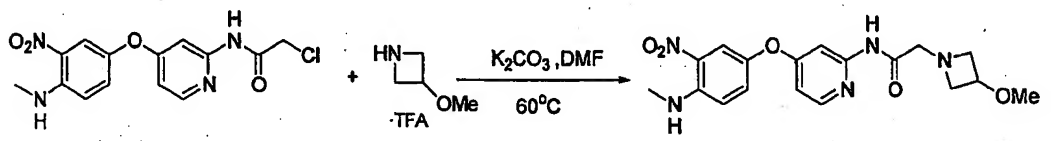
Example 67

Synthesis of N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(3-methoxyazetidin-1-yl)acetamide

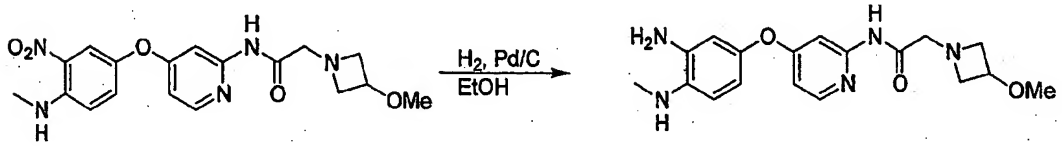




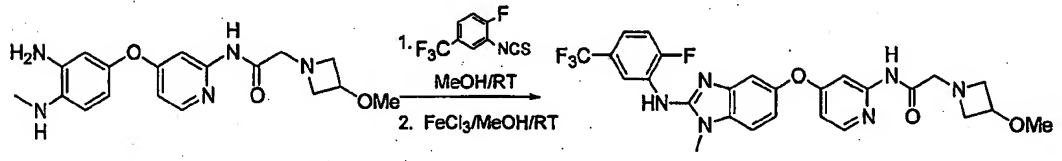
1-N-Boc-3-hydroxyazetidine (1.0 eq) in THF (10 mL) was added to NaH (2.6 eq) in THF (20 mL) at 0°C. After 20 min, MeI (1.1 eq) was added dropwise. This mixture stirred for 2 h and was then quenched with H_2O and extracted twice with EtOAc. The organic layer was dried over sodium sulfate and concentrated. MS: MH^+= 132.1 (MH^+-*t*-Bu). The material was dissolved in CH_2Cl_2 and TFA (3:1) and stirred overnight. The solvent was then removed by rotary evaporation to give a clear oil. MS: MH^+= 87.9.



MS: MH^+= 388.1.



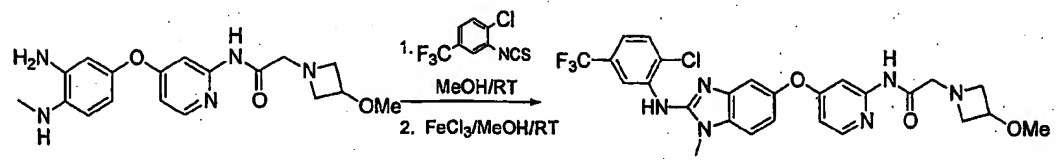
MS: MH^+= 358.2.



MS: MH^+= 545.1.

Example 68

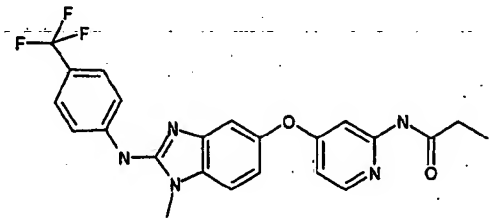
Synthesis of N-{4-[(2-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(3-methoxyazetidin-1-yl)acetamide



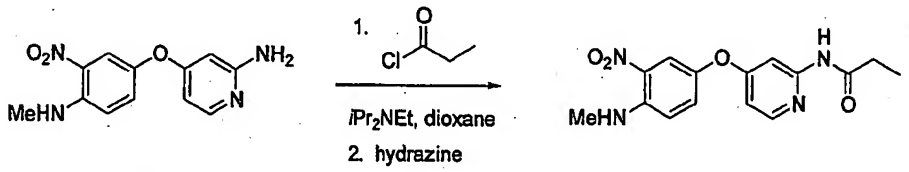
MS: MH^+= 561.1.

Example 69

Synthesis of N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}propanamide



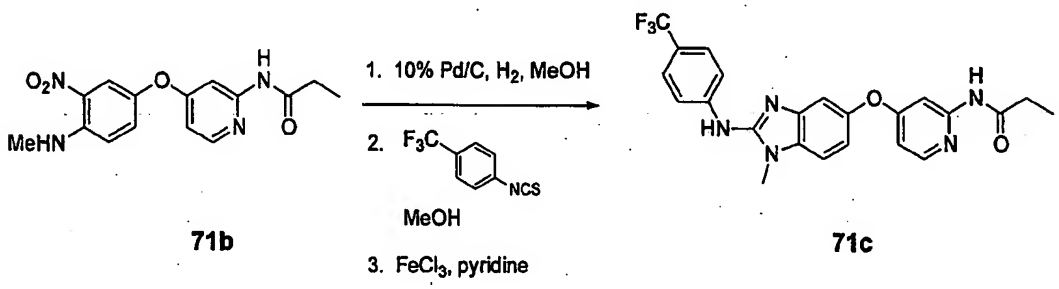
1. Synthesis of N-[4-(4-Methylamino-3-nitro-phenoxy)-pyridin-2-yl]-propionamide



71a 71b

To a stirring suspension of **71a** (1 eq) and *i*Pr_2NEt (1.5 eq) in dioxane (4 mL) was added propionyl chloride (2 eq) and mainainted at rt overnight. Hydrazine (1 eq) was added and stirred for 2 hours. Crude product was concentrated down, and was then partitioned between EtOAc and saturated aqueous Na_2CO_3. The layers were separated and the aqueous layer was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried (MgSO4), concentrated, and the resulting residue was adsorbed onto SiO_2. Purification by flash chromatography (0.5 : 99.5, 0.75 : 99.25, 1 : 99, 2 : 98, methanol-CH_2Cl_2) gave 310 mg of a bright orange solid as **71b**: ^{1}H NMR (300 MHz, $CDCl_3$) □ 8.35 (br s, 1 H), 8.13 (d, *J* = 5.77 Hz, 1 H), 7.91 (d, *J* = 2.74 Hz, 1 H), 7.68 (d, *J* = 2.2 Hz, 1 H), 7.38 (dd, *J* = 2.74, 2.75 Hz 1 H), 7.11 (d, *J* = 9.61 Hz, 1 H), 6.68 (dd, *J* = 2.47, 2.47 Hz, 1 H), 3.065 (d, *J* = 3.85 Hz, 3 H), 2.40 (m, 2 H), 1.141 (m, 3 H).

2. Synthesis of N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}propanamide



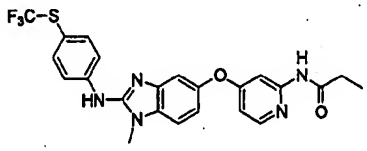
71b 71c

A suspension of propionamide **71b** (1 eq) and 10% Pd/C (10 mol %) in methanol (4 mL) was charged with H_2 and the resulting reaction mixture was maintained under a H_2 atmosphere for 1 h at rt. The mixture was filtered and the remaining solids washed thoroughly with EtOAc and methanol. The combined organic portions were evaporated to afford 272 mg of a brown residue as the phenylene diamine, which was carried forward without further purification.

The above diamine (1 eq) was dissolved in methanol (2 mL) and 4-trifluoromethyl phenylthioisocyanate (1 eq) was added. The reaction was maintained for 16 h. Pyridine (3 eq) was added to the reaction, followed by ferric chloride (1.1 eq). The resulting dark reaction mixture was maintained at rt for 16 h, then suspended in saturated aqueous Na_2CO_3 solution, and filtered with Celite. The remaining solids were washed with EtOAc and the combined filtrate was partitioned and separated. The aqueous portion was extracted with EtOAc (3 X) and the combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated. Purification by semi-prep HPLC gave **71c** as the TFA salt. LCMS *m/z* 456.2 (MH^+), t_R = 3.21 min.

Example 70

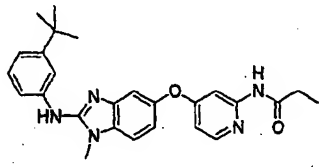
Synthesis of N-(4-{[1-methyl-2-({4-[(trifluoromethyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)propanamide



Synthesized as described above in Example 69 using 4-trifluoromethylphenyl isothiocyanate. LCMS *m/z* 488.2 (MH^+), R_t 3.72 min.

Example 71

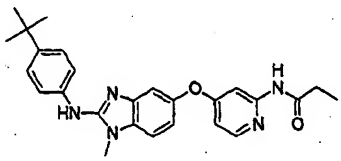
Synthesis of N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]propanamide



Synthesized as described above in Example 69 using 3-*tert*-butylphenyl isothiocyanate. LCMS *m/z* 444.3 (MH^+), R_t 3.47 min.

Example 72

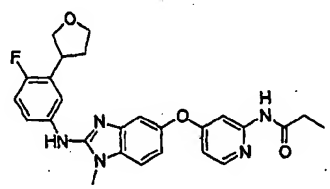
Synthesis of N-[4-({2-[(4-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]propanamide



Synthesized as described above in Example 69 using 4-*tert*-butylphenyl isothiocyanate. LCMS *m/z* 444.3 (MH^+), R_t 3.52 min.

Example 73

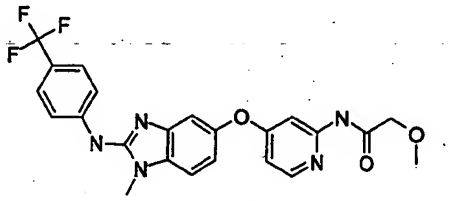
Synthesis of N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]propanamide



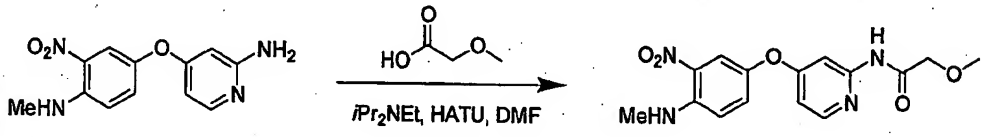
Synthesized as described above in Example 69 using 3-(2-fluoro-5-isothiocyanato-phenyl)-tetrahydro-furan. LCMS *m/z* 476.3 (MH^+), R_t 2.73 min.

Example 74

Synthesis of 2-methoxy-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



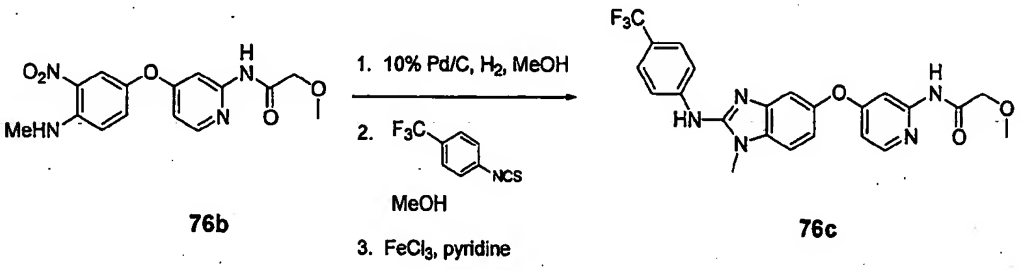
1. Synthesis of 2-Methoxy-N-[4-(4-methylamino-3-nitro-phenoxy)-pyridin-2-yl]-acetamide



76a **76b**

To a solution of iPr_2NEt (6 eq) and dry DMF (8 mL) was added methoxyacetic acid (2 eq). The resulting solution maintained at rt for 30 min, at which time HATU (2.2 eq) was added, and continued stirring at rt for 1 hour. **76a** (1 eq) was added, the flask was sealed and the resulting solution was heated to 50 °C overnight. Crude product was partitioned between EtOAc and water, the layers were separated and the aqueous layer was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried (MgSO4), concentrated, and the resulting residue was adsorbed onto SiO_2. Purification by flash chromatography (0.5 : 99.5, 0.75 : 99.25, 1 : 99, 2 : 98, methanol-CH_2Cl_2) gave 640 mg of a bright orange solid as **76b**: ^1H NMR (300 MHz, $CDCl_3$) □ 8.67 (br s, 1 H), 8.15 (d, J = 5.76 Hz, 1 H), 8.04 (br s, 1 H), 7.965 (d, J = 2.75 Hz, 1 H), 7.807 (d, J = 2.2 Hz 1 H), 7.30 (dd, J = 2.75, 2.75 Hz, 1 H), 6.916 (d, J = 9.34 Hz, 1 H), 6.63 (dd, J = 2.47, 2.48 Hz, 1 H), 3.98 (s, 2 H), 3.48 (s, 3 H), 3.06 (d, J = 5.22 Hz, 3 H).

2. Synthesis of 2-methoxy-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide



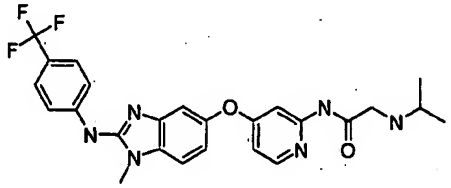
76b **76c**

A suspension of methoxyacetamide **76b** (1 eq) and 10% Pd/C (10 mol %) in methanol (4 mL) was charged with H_2 and the resulting reaction mixture was maintained under a H_2 atmosphere for 1 h at rt. The mixture was filtered and the remaining solids washed thoroughly with EtOAc and methanol. The combined organic portions were evaporated to afford 272 mg of a brown residue as the phenylene diamine, which was carried forward without further purification.

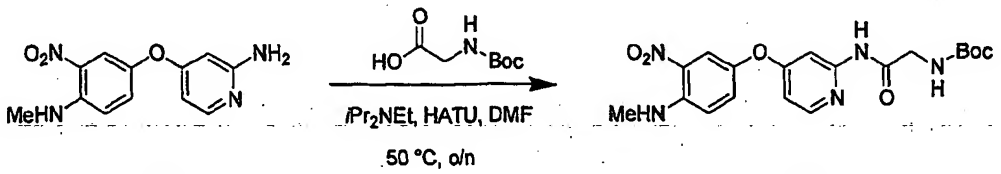
The above diamine (1 eq) was dissolved in methanol (2 mL) and 4-trifluoromethyl phenylthioisocyanate (1 eq) was added. The reaction was maintained for 16 h. Pyridine (3 eq) was added to the reaction, followed by ferric chloride (1.1 eq). The resulting dark reaction mixture was maintained at rt for 16 h, then suspended in saturated aqueous Na_2CO_3 solution, and filtered with Celite. The remaining solids were washed with EtOAc and the combined filtrate was partitioned and separated. The aqueous portion was extracted with EtOAc (3 X) and the combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated. Purification by semi-prep HPLC gave **76c** as the TFA salt. LCMS *m/z* 474.2 (MH^+), t_R = 2.24 min.

Example 75

Synthesis of N~2~-isopropyl-N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide



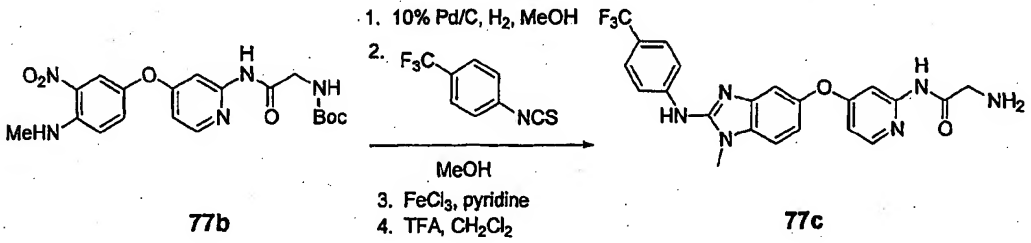
1. Synthesis of {[4-(4-Methylamino-3-nitro-phenoxy)-pyridin-2-ylcarbamoyl]-methyl}-carbamic acid tert-butyl ester



77a 77b

To a solution of *i*Pr$_2$NEt (4.5 eq) and dry DMF (75 mL) was added tert-Butoxycarbonylamino-acetic acid (1.5 eq). The resulting solution maintained at rt for 30 min, at which time HATU (2 eq) was added, and continued stirring at rt for 1 hour. **77a** (1 eq) was added, the flask was sealed and the resulting solution was heated to 50 °C overnight. Crude product was partitioned between EtOAc and water, the layers were separated and the aqueous layer was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried (MgSO4), concentrated, and the resulting residue was adsorbed onto SiO_2. Purification by flash chromatography (0.5 : 99.5, 0.75 : 99.25, 1 : 99, 2 : 98, methanol-CH_2Cl_2) gave 4.11 g of a bright orange solid as **77b.**

2. Synthesis of 2-Amino-N-{4-[1-methyl-2-(4-trifluoromethyl-phenylamino)-1H-benzoimidazol-5-yloxy]-pyridin-2-yl}-acetamide



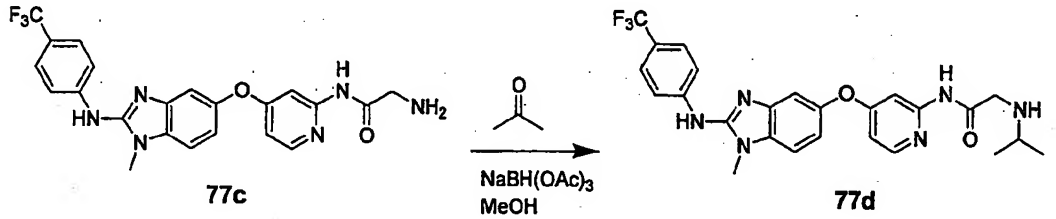
77b 77c

A suspension of **77b** (1 eq) and 10% Pd/C (10 mol %) in methanol (4 mL) was charged with H_2 and the resulting reaction mixture was maintained under a H_2 atmosphere for 1 h at rt. The mixture was filtered and the remaining solids washed thoroughly with EtOAc and methanol. The combined organic portions were evaporated to afford 380 mg of a brown residue as the phenylene diamine, which was carried forward without further purification.

The above diamine (1 eq) was dissolved in methanol (2 mL) and 4-trifluoromethyl phenylthioisocyanate (1 eq) was added. The reaction was maintained for 16 h. Pyridine (3 eq) was added to the reaction, followed by ferric chloride (1.1 eq). The resulting dark reaction mixture was maintained at rt for 16 h, then suspended in saturated aqueous Na_2CO_3 solution, and filtered with Celite. The remaining solids were washed with EtOAc and the combined filtrate was partitioned and separated. The aqueous portion was extracted with EtOAc (3 X) and the combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated.

The above glycine-amide (1 eq was dissolved in CH_2Cl_2 (1 mL) and trifluoroacetic acid (10 eq) was added. The resulting solution was maintained at rt for 16 h. Crude product was concentrated down, and then neutralized with saturated aqueous Na_2CO_3 solution. The aqueous portion was extracted with EtOAc (3 X) and the combined organic portions were washed with brine, dried ($MgSO_4$), and evaporated to give 20 mg of **77c** as a brownish semi-solid.

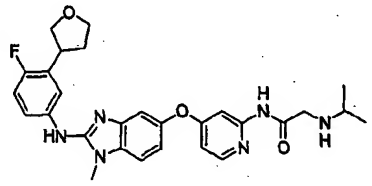
3. Synthesis of N~2~~isopropyl-N~1~~{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]-amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide



A solution of **77c** (1 eq) and acetone (2 eq) in MeOH (100 *u*L) was maintained at rt for 30 min. $NaBH(OAc)_3$ (3 eq) was added and resulting suspension continued stirring for 30 min. Crude product was concentrated down, then partitioned between EtOAc and water, the layers were separated and the aqueous layer was extracted with EtOAc (3 X). The combined organic portions were washed with brine, dried (MgSO4), concentrated. Resulting residue was dissolved in DSMO and purified on semi-prep HPLC to give **77d** as the TFA salt. LCMS *m/z* 499.1 (MH^+), t_R = 2.00 min.

Example 76

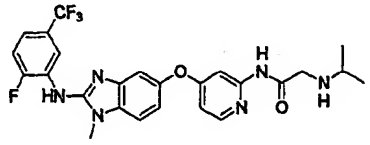
Synthesis of N~1~-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-isopropylglycinamide



Synthesized as described above in Example 75 using 3-(2-fluoro-5-isothiocyanato-phenyl)-tetrahydro-furan. LCMS *m/z* 519.2 (MH^+), R_t 1.80 min.

Example 77

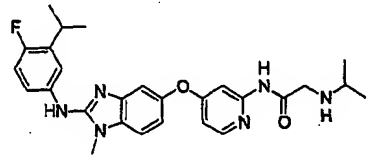
Synthesis of N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~-isopropylglycinamide



Synthesized as described above in Example 75 using 2-fluoro-5-trifluoromethylphenyl isothiocyanate. LCMS *m/z* 517.3 (MH^+), R_t 2.02 min.

Example 78

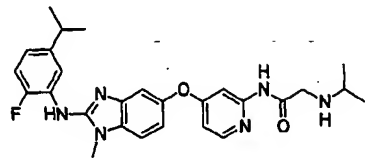
Synthesis of N~1~-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-isopropylglycinamide



Synthesized as described above in Example 75 using 4-fluoro-3-isopropylphenyl isothiocyanate. LCMS *m/z* 491.2 (MH^+), R_t 2.05 min.

Example 79

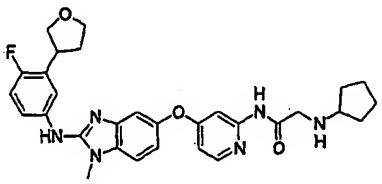
Synthesis of N~1~-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-isopropylglycinamide



Synthesized as described above in Example 75 using 2-Fluoro-5-isopropylphenyl isothiocyanate. LCMS *m/z* 491.2 (MH^+), R_t 2.09 min.

Example 80

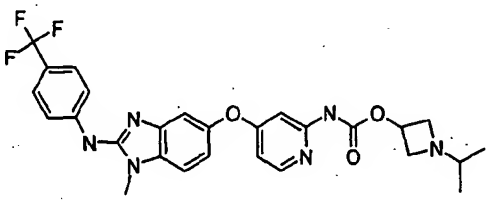
Synthesis of N~2~-cyclopentyl-N~1~-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide



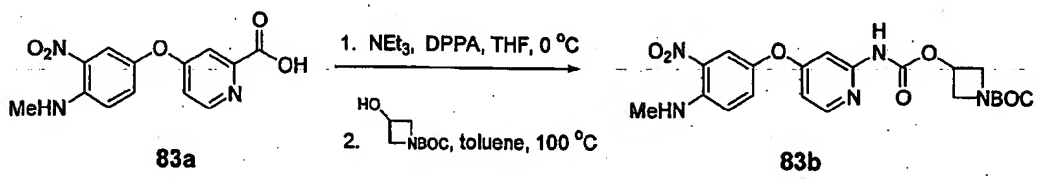
Synthesized as described above in Example 75 using cyclopropanone and 3-(2-fluoro-5-isothiocyanato-phenyl)-tetrahydro-furan. LCMS *m/z* 545.1 (MH^+), R_t 2.86 min.

Example 81

Synthesis of 1-isopropylazetidin-3-yl 4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-ylcarbamate



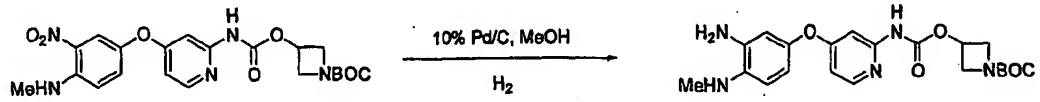
Step 1: Synthesis of 3-[4-(4-Methylamino-3-nitro-phenoxy)-pyridin-2-ylcarbamoyloxy]-azetidine-1-carboxylic acid tert-butyl ester



83a 83b

To a suspension of acid **1** (1 eq.) in dry THF (10 mL) at 0 °C was added triethylamine (3.0 eq.) and the resulting reaction was maintained at 0 °C for 45 min to afford a homogenous solution. Diphenylphosphoryl azide (DPPA, 1.1 eq) was added and the reaction was maintained o/n allowing the cooling bath to expire. The reaction was concentrated and the resulting residue dissolved in CH_2Cl_2. The organic portion was washed with saturated $NaHCO_3$ (3 X) and the combined aqueous phases were extracted with CH_2Cl_2. The combined organic portions were dried ($MgSO_4$), filtered, and concentrated. The remaining residue was suspended in toluene. To this suspension was added *N*-BOC azetidin-2-ol (1 eq) and the reaction mixture was heated to and maintained at 100 °C for 1h. The reaction was then allowed to cool to rt and concentrated. The residue was dissolved in CH_2Cl_2 and washed with saturated Na_2CO_3 (3 X). The combined aqueous phases were extracted with CH_2Cl_2 and the combined organic layers were washed with Na_2CO_3 and brine, dried ($MgSO_4$), and evaporated. The crude residue was adsorbed onto SiO_2 and purified by flash chromatography (9 : 1, 4 : 1, 2 : 1, 1 : 1 hexanes-EtOAc) to furnish 625 mg (70%) of a light orange solid as **2**: 1H NMR (300 MHz, $CDCl_3$) δ 9.32 (br, s, 1 H), 8.17 (d, J = 6.0 Hz, 1 H), 8.06 (br dd, J = 5.0, 10.2 Hz, 1 H), 7.96 (d, J = 2.8 Hz, 1 H), 7.52 (d, J = 2.5 Hz, 1 H), 7.30 (dd, J = 2.8, 9.2 Hz, 1 H), 6.93 (d, J = 9.2 Hz, 1 H), 6.57 (dd, J = 2.5, 6.0 Hz, 1 H), 5.18 (dddd, J = 4.4, 4.4, 6.9, 6.9 Hz, 1 H), 4.25 (ddd, J =0.8, 6.9, 10.1 Hz, 2 H), 3.94 (ddd, J = 0.8, 4.4, 10.1 Hz, 2 H), 3.07 (d, J = 5.2 Hz, 3 H), 1.43 (br s, 9 H).

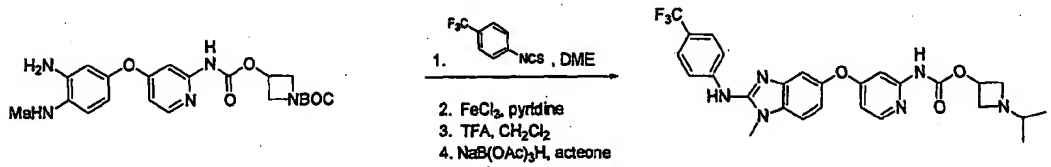
Step 2: Synthesis of 3-[4-(3-Amino-4-methylamino-phenoxy)-pyridin-2-ylcarbamoyloxy]-azetidine-1-carboxylic acid tert-butyl ester



83b 83c

A suspension of nitroaniline **83b** (1 eq.) in dry MeOH (8 mL) was sparged with argon over 20 min. 10% Pd/C (0.1 eq) was added in one portion and the reaction vessel sealed with a three-way stopcock fitted with a balloon filled with hydrogen. The reaction mixture was purged with hydrogen and the reaction maintained at rt over 3h. The reaction was filtered through Celite and the filtrate was concentrated to give 474 mg (94%) of a brown residue as **83c**. The material was carried forward without further purification: LCMS *m/z* 430.3 (MH^+), t_R = 2.07 min.

Step 3: 1-isopropylazetidin-3-yl 4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-ylcarbamate



83c 83d

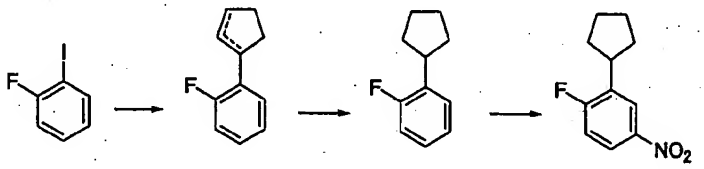
4-Trifluoromethyl phenylthioisocyanate (1.3 eq.) was added to a solution of diamine **83c** (1 eq.) in dry DME (10 mL) and the reaction was maintained at rt for 14 h. Pyridine (3 eq.) was added and the reaction cooled to 0 °C. $FeCl_3$ (1.2 eq.) was added in one portion and the resulting reaction was maintained at 0 °C for 5 min, then at rt for 12 h. The reaction was concentrated and partitioned with EtOAc and saturated Na_2CO_3. The resulting mixture was filtered through Celite and the remaining solids washed with EtOAc. The combined phases were then partitioned and separated. The organic phase was washed with saturated Na_2CO_3 (3 X) and the combined aqueous portions were extracted with EtOAc. The combined organic portions were washed with brine, dried ($MgSO_4$), and concentrated. The crude residue was adsorbed onto SiO_2 and purified by flash chromatography (2 : 1 hexanes-acetone). The resulting material was dissolved in

CH_2Cl_2 (4 mL), treated with TFA (1 mL) and the resulting reaction maintained at rt for 2 h. The reaction was concentrated and partitioned with CH_2Cl_2 and saturated Na_2CO_3. The organic phase was washed with saturated Na_2CO_3 (3 X) and the combined aqueous portions were extracted with CH_2Cl_2 (3 X). The combined organic phases were dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in MeOH (2 mL) and treated with an excess of acetone and $NaB(OAc)_3H$. The reaction was maintained at rt for 14 h and then concentrated. The residue was then suspended in EtOAc and washed with aqueous 0.5 N HCl solution (3 X). The combined acidic aqueous phases were made basic (pH = 8) by addition of 1 N NaOH solution. The resulting cloudy aqueous phase was extracted with EtOAc (3 X) and the combined organic portions were dried ($MgSO_4$) and concentrated. The resulting residue was further purified by preparative HPLC and reconstituted as the mono mesylate salt to afford 72 mg of 2 as a white solid: ^{1}H NMR (300 MHz, CD_3OD) δ 8.10 (d, J = 5.9 Hz, 1 H), 7.73 (d, J = 8.9 Hz, 2 H), 7.69 (d, J = 8.9 Hz, 2 H), 7.49 (d, J = 8.7 Hz, 1 H), 7.38 (d, J = 2.2. Hz, 1 H), 7.19 (d, J = 2.2 Hz, 1 H), 7.03 (dd, J = 2.2 8.7 Hz, 1 H), 6.65 (dd, J = 2.2, 5.9 Hz, 1 H), 5.19 (m, 1 H), 4.50 (app dd, J = 6.8, 11.7 Hz, 2 H), 4.24 (app dd, J = 4.9, 11.7 Hz, 2 H), 3.49 (dddd, J = 6.6, 6.6, 6.6, 6.6 Hz, 1 H), 2.69 (s, 3 H), 1.24 (d, J = 6.6 Hz, 6 H); LCMS m/z 541.1 (MH^+), t_R = 2.03 min.

Example 82

Synthesis of various intermediates for use in the benzimidazole ring formation are described in this example.

Example 82a. 4-fluoro-3-cyclopentyl-1-nitrobenzene



In a steel pressure vessel with stirbar, sodium acetate (4eq), tetrabutylammonium bromide (1 eq) and $Pd(dppf)Cl_2$-CH_2Cl_2 (.03 eq) were suspended in DMA (dimethylacetamide, 0.2M). Nitrogen was bubbled through 10 minutes, then 2-fluoro-1-iodobenzene (1 eq) and cyclopentene (5eq) were added. The vessel was sealed and heated at 140°C, 14hrs. The vessel was then cooled to RT, the contents were diluted (ethyl

acetate), washed successively with water (2x), aq. $NaHCO_3$, NaCl, then dried over anhydrous K_2CO_3, filtered and stripped to an oil. Chromatography (3%ethyl acetate in hexanes on silica gel) provides a pale green oil as a mixture of olefin isomers (83%).

Hydrogenation over palladium on carbon (.5gm 10%w/w) in methanol (60 mL) at 80 psig and RT converts both to a single, volatile alkane 2'fluorophenylcyclopentane.

A solution of 2'fluorophenylcyclopentane in acetic anhydride (0.2M) was cooled to –10°C. Sulfuric acid (to make 1%v/v) was added. Followed by nitric acid (1.15 eq), dropwise. After addition was complete, the reaction was allowed to warm to RT. After 30 min at RT, TLC showed complete reaction. The mixture was poured onto ice, extracted into ethyl acetate 2x. The combined extracts were washed successively with water, aq. $NaHCO_3$, NaCl, then dried over anhydrous K_2CO_3, filtered and stripped to an oil. Flash chromatography (3% ethyl acetate in hexanes on silica gel) provides 4-fluoro-3-cyclopentyl-1-nitrobenzene (48% yield)

Example 82b. Synthesis of 1-tert-butyl-4-fluorobenzene

In a steel bomb were combined 4-tert-butyl aniline (1eq) and 70% hydrogen fluoride-pyridine (25g/gm aniline). Sodium nitrite (1.5eq) was then added portion wise over 5 minutes. The resulting solution was allowed to stir for 1h at room temperature and then the bomb was sealed and heated at 85°C for 1h. Solution was then quenched with water/ice and extracted with ethyl ether. Organics washed with brine and dried with sodium sulfate and concentrated to afford 1-tert-butyl-4-fluorobenzene.

^{1}H NMR (DMSO, δ ppm): 1.22(9H, s), 7.07 (2H, t), 7.38 (2H, dd)

Example 82c. Synthesis of 4-tert-butyl-1-fluoro-2-nitrobenzene

1-tert-butyl-4-fluorobenzene (1eq) was dissolved in concentrated sulfuric acid (1.65M) and cooled to 0°C in an ice/water bath. Potassium nitrate(1eq) was then added in small portions as to allow the temperature of the reaction not to exceed 7°C. After complete addition the mixture was allowed to stir for an additional 30 minutes, then poured onto ice/water and extracted with ethyl acetate. Organics were washed with a saturated solution of sodium bicarbonate, brine and dried with sodium sulfate and concentrated. Crude mixture was purified by flash chromatography on silica.

(85%Hex:15%EtOAc) to afford 4-tert-butyl-1-fluoro-2-nitrobenzene.

^{1}H NMR ($CDCl_3$, δ ppm): 1.3(9H, s), 7.2(1H, dd), 7.62(1H, ddd), 8.03(1H, dd)

Example 82d. Synthesis of 5-tert-butyl-2-fluorobenzenamine

To 4-tert-butyl-1-fluoro-2-nitrobenzene in methanol was added a catalytic amount of palladium on carbon (10%). The mixture was allowed to stir for 1h at room temperature under an atmosphere of hydrogen. Mixture was filtered though celite and concentrated to afford 5-tert-butyl-2-fluorobenzenamine.

MS: MH^+ =168

Example 82e. Synthesis of 1-(2-fluoro-5-nitrophenyl)ethanone

In a 3-neck flask equipped with an internal thermometer was added sulfuric acid and cooled to –10°C in an ice/salt/water batch. 2'-fluoroacetophenone(1eq) in sulfuric acid was added dropwise over 10 minutes via addition funnel to produce a solution of 0.2M. Nitric acid (1.15eq) in sulfuric acid was then added dropwise at a rate not to exceed 5°C. After complete addition resulting solution was allowed to stir at for 30 minutes. Solution was poured onto ice and extracted with ethyl acetate. Organics were washed with a saturated solution of sodium bicarbonate, brine, dried with sodium sulfate and concentrated. Crude product was purified using flash chromatography (85%Hex:15%EtoAc) on silica to afford 1-(2-fluoro-5-nitrophenyl)ethanone.

^{1}H NMR ($CDCl_3$, δ ppm): 2.7(3H,s), 7.28(1H,t), 8.4(1H,m), 8.8(1H,dd)

Example 82f. Synthesis of 1-fluoro-4-nitro-2-(prop-1-en-2-yl)benzene

KHMDS(1eq) in toluene is added dropwise over 5 minutes to a stirred suspension of triphenylphosphinemethyl bromide(1.2eq) in THF at –78°C under nitrogen. After complete addition solution is allowed to warm to room temperature for 5 minutes then cooled a second time to –78°C. 1-(2-fluoro-5-nitrophenyl)ethanone(1eq) in THF is then added via cannulla into the cold suspension over 10 minutes. Resulting mixture is then allowed to warm to room temperature and stirred for 1h. Solvent is then removed under reduced pressure, cyclohexane is then added and mixture heated briefly to reflux, cooled to room temperature, filtered and filtrate concentrated. Crude product is purified using flash chromatography(85%Hex:15%EtoAc) on silica to afford 1-fluoro-4-nitro-2-(prop-1-en-2-yl)benzene.

^{1}H NMR ($CDCl_3$, δ ppm): 2.15(3H,s), 5.25(2H,d), 7.19(1H,t), 8.1(1H,m), 8.2(1H,dd)

Example 82g. Synthesis 2-(2-fluoro-5-nitrophenyl)-2-methyloxirane

1-fluoro-4-nitro-2- (prop-1-en-2-yl) benzene (1eq) was dissolved in dichloromethane and cooled to $-10^{o}C$ using and ice/salt/water bath under nitrogen. MCPBA (1.5eq) in dichloromethane was then added dropwise and resulting solution allowed to warm to room temperature and allowed to stir 48h. Solution was quenched with 10% sodium sulfite, neutralized with saturated solution of sodium bicarbonate, extracted with dichloromethane. Organics were washed with brine, dried with sodium sulfate and concentrated. Crude product was purified with flash chromatography (85%Hex: 15%EtoAc) to afford 2-(2-fluoro-5-nitrophenyl)-2-methyloxirane.

^{1}H NMR ($CDCl_3$, δ ppm): 1.7(3H,s), 2.8(1H, d), 3.05(1H,d), 7.2(1H, t), 8.2(1H,m), 8.35(1H,dd)

Example 82h. Synthesis of 2-(2-fluoro-5-nitrophenyl) propanal

2-(2-fluoro-5-nitrophenyl)-2-methyloxirane (1eq) was dissolved in ethyl ether (1mL) under nitrogen. BF_3-etherate (0.87eq) was added dropwise at room temperature and after complete addition solution was allowed to stir for 1h. Solution was then quenched with water, extracted with ethyl ether. Organics washed with brine, dried with sodium sulfate and concentrated. Crude product was purified using flash chromatography (85%Hex: 15%EtOAc) on silica to afford 2-(2-fluoro-5-nitrophenyl) propanal.

^{1}H NMR ($CDCl_3$, δ ppm): 1.5(3H,d), 3.9(1H,c), 7.2(1H,t), 8.15(1H,dd), 8.21(1H,m), 9.7(1H,s)

Example 82i. Synthesis of 2-(2-fluoro-5-nitrophenyl)-2-methylpent-4-enal

To a solution of palladium acetate (0.1eq), triphenylphosphine (0.2eq), lithium chloride (1.0eq) in THF were sequentially added 2-(2-fluoro-5-nitrophenyl) propanal (1.1eq) in THF, allyl alcohol (1.0eq), triethylamine (1.2eq) and triethylborane (2.4eq) under nitrogen at room temperature. Solution was allowed to stir for 2h. Mixture was diluted with saturated solution of sodium bicarbonate, extracted with ethyl acetate. Organics were washed with brine, dried with sodium sulfate and concentrated. Crude product was purified using flash chromatography (85%Hex: 15%EtoAc) on silica to afford 2-(2-fluoro-5-nitrophenyl)-2-methylpent-4-enal.

^{1}H NMR ($CDCl_3$, δ ppm): 1.5(3H, s), 2.6-2.85(2H, m), 5.1(2H,m), 5.5(1H,m), 7.2(1H,t), 8.2(2H,m), 9.7(1H,d)

Example 82j. Synthesis of 2-(2-fluoro-5-nitrophenyl)-2-methylbutane-1,4-diol

2-(2-fluoro-5-nitrophenyl)-2-methylpent-4-enal(1eq) was dissolved in dichloromethane:methanol (3:1) and cooled to –78°C. Ozone was then bubbled through the solution until a blue color was noticed. Air was then passed through the solution followed by the addition of sodium borohydride(5eq). Resulting solution was allowed to warm to room temperature and diluted with brine, extracted with dichloromethane. Organics were dried with sodium sulfate and concentrated to afford 2-(2-fluoro-5-nitrophenyl)-2-methylbutane-1,4-diol. The product was used in the next step with no further characterization.

Example 82k. Synthesis of 3-(2-fluoro-5-nitrophenyl)-tetrahydro-3-methylfuran

To a solution of triphenylphosphine(2eq) in dichloromethane at 0°C under nitrogen was added dropwise triflic anhydride(1eq). After 15 minutes 2-(2-fluoro-5-nitrophenyl)-2-methylbutane-1,4-diol(1eq)was added in dichloromethane followed by potassium carbonate(1eq). The resulting mixture was allowed to warm to room temperature for 5h. To the mixture was added water and extracted with dichloromethane. The organic layer was washed with brine and dried with sodium sulfate and concentrated. Crude product was purified using flash chromatography (85%Hex:15%EtoAc) on silica to afford 3-(2-fluoro-5-nitrophenyl)-tetrahydro-3-methylfuran.

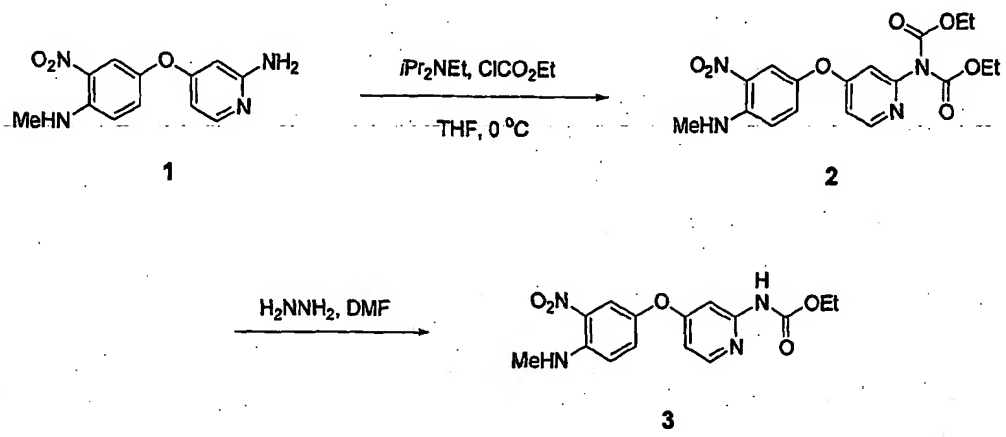
^{1}H NMR ($CDCl_3$, δ ppm): 1.45(3H,s), 2.2-2.4(2H,m), 3.85(1H,d), 3.9-4.05(3H,m), 7.2(1H,t), 8.15(2H,m)

Example 82l. Synthesis of 4-fluoro-3-(tetrahydro-3-methylfuran-3-yl)benzenamine

To 3-(2-fluoro-5-nitrophenyl)-tetrahydro-3-methylfuran in methanol was added a catalytic amount of palladium on carbon (10%). The mixture was allowed to stir for 1h at room temperature under hydrogen atmosphere. Mixture was filtered though celite and concentrated to afford 4-fluoro-3-(tetrahydro-3-methylfuran-3-yl)benzenamine.

MS: $MH^+ = 196$

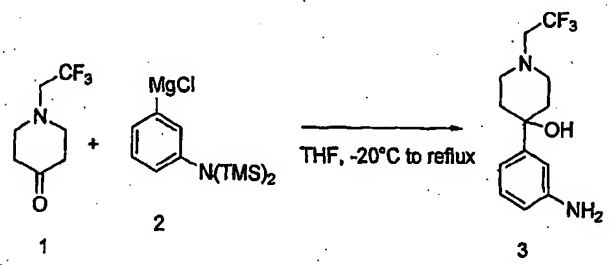
Example 82m. Preparation of [4-(4-methylamino-3-nitro-phenoxy)-pyridin-2-yl]-carbamic acid ethyl ester



1 2 3

Ethyl chloroformate (2 eq.) was added to a stirring solution of aniline **1** (1 eq.) and iPr$_2$NEt (2 eq.) in dry THF (14 mL) at 0 °C. The reaction was allowed to warm to rt over 2 h. The reaction concentrated and the resulting residue dissolved in EtOAc. The organic phase was washed with saturated aqueous $NaHCO_3$ (3 X) and the combined aqueous portions were extracted with EtOAc. The combined organic portions were concentrated to give an orange residue as **2**. The residue was dissolved in DMF (20 mL), hydrazine monohydrate (1 eq.) added and the resulting reaction maintained at rt for 14 h. The reaction volume was reduced and the remaining solution was partitioned between EtOAc and water. The layers were separated and the aqueous phase extracted with EtOAc (3 X). The combined organic layers were concentrated to give an orange solid as **3** which was carried forward without further purification: LCMS m/z 333.3 (MH^+), t_R = 2.29 min.

Example 82n. Synthesis of 4-(3-aminophenyl)-1-(2,2,2-trifluoroethyl)piperidin-4-ol (3)

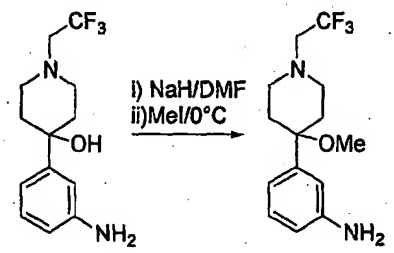


1 2 3

1 equivalent of known compound 1 (WO 9521452) as a 1M solution in dry THF was cooled to –20°C under argon. 1.1 Equivalents of grignard compound 2 (Aldrich) as a 2M solution in THF was then added dropwise via syringe. Reaction stirred at –20°C for 20mins, allowed to warm to room temperature, then briefly refluxed.

Solution was then cooled in an ice bath and an excess of dilute aqueous HCl was carefully added. An aqueous solution of sodium bicarbonate was added to bring the pH >7 and the product was extracted with ethyl acetate. Removal of organic solvent *in vacuo* gave a residue that was purified via silica gel column chromatography (30% ethyl acetate in hexane). Compound 3 was then further purified by recrystallizing from a hexane/ethyl acetate solution to give a clear oil in a 75% yield. LCMS *m/z* 275.3 (MH^+)

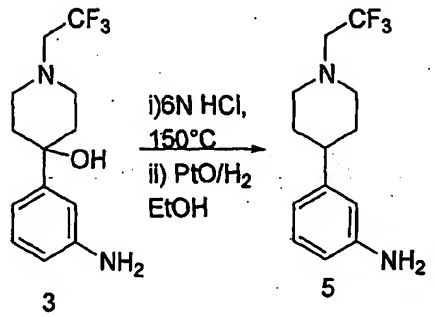
Example 82o. Synthesis of 3-[4-Methoxy-1-(2,2,2-trifluoro-ethyl)-piperidin-4-yl]-phenylamine



3 4

To Compound 3 (1eq) in dry DMF as a 1M solution was added 1.1eq of sodium hydride at room temperature. This solution was allowed to react for 30mins. The solution was then cool to 0°C and 1.1 eq of methyl iodine added. Reaction was then slowly warmed to room temperature where water was added. The product was extracted with ethyl acetate, washed with water, dried over magnesium sulfate, and the solvent removed to give Compound 4 in sufficient purity. LCMS *m/z* 289.3 (MH^+).

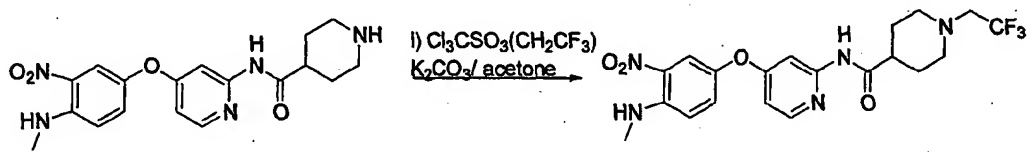
Example 82p. Synthesis of 3-[1-(2,2,2-Trifluoro-ethyl)-piperidin-4-yl]-phenylamine.



3 5

Compound 3 was heated to 150°C in a 6N HCl solution via a microwave reactor for 5mins. Solution was neutralized and extracted with ethyl acetate. After removal of solvent, the intermediate was dissolved in ethanol and reduced over PtO in a hydrogen gas atmosphere. The catalyst was removed by filtering through celite and the ethanol evaporated to give Compound 5.

Example 82q. Synthesis of 1-(2,2,2-Trifluoro-ethyl)-piperidine-4-carboxylic acid [4-(4-methylamino-3-nitro-phenoxy)-pyridin-2-yl]-amide

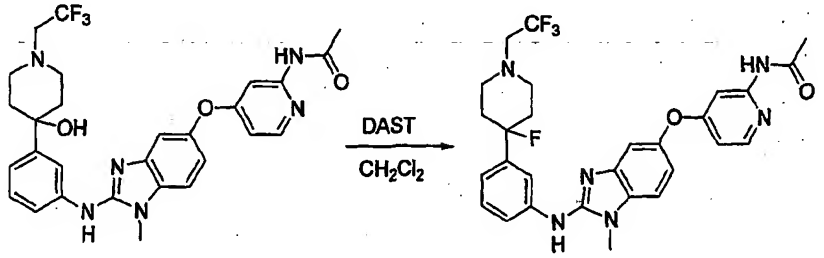


1 2

To 1 eq. of Compound 1 in acetone as a 1M solution and 4 eq. Of potassium carbonate was added 1eq of 2,2,2-trifluoromethyl trichloromethansulfonate. Solution briefly refluxed, cooled, solvent removed and residue partitioned between water and ethyl acetate. Organic separated, dried over magnesium sulfate, solvent evaporated to provide 2.

Example 83

Synthesis of N-(4-{[2-({3-[4-fluoro-1-(2,2,2-trifluoroethyl)piperidin-4-yl]phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide



85a 85b

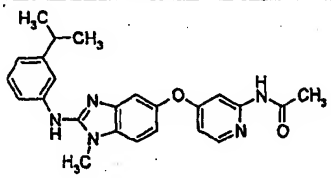
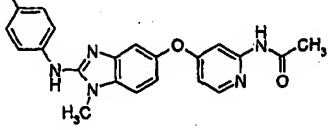
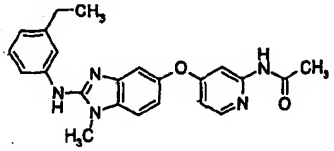
Compound **85a** (1 eq) was dissolved in dichloromethane to a 1M solution under argon. DAST (Aldrich), 1 eq., was then added and solution allowed to react for 1hr.

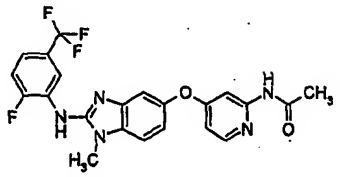
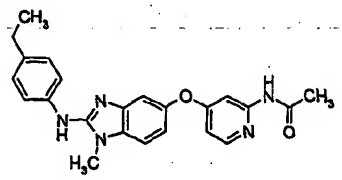
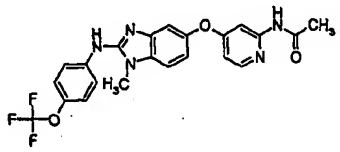
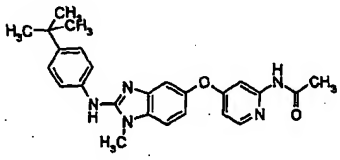
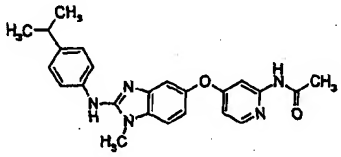
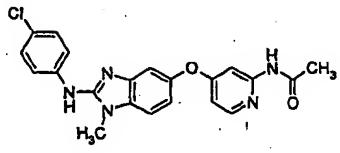
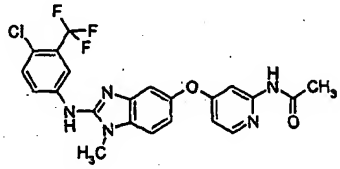
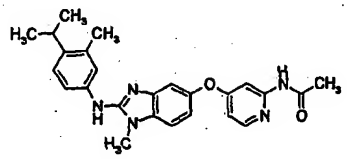
Water was added, the phases separated, and the organic solvent removed *in vacuo*. The residue was purified via silica gel column chromatography (5% MeOH/DCM) to give Compound **85b** in nearly quantitative yield. LCMS *m/z* 557.5 (MH^+), R_t 1.61 min.

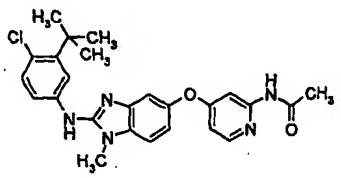
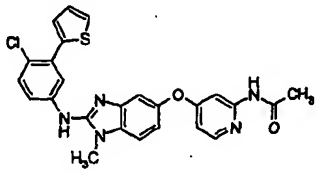
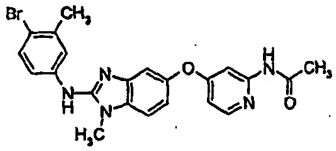
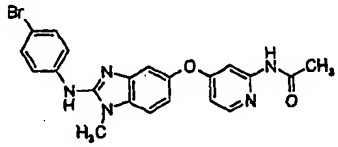
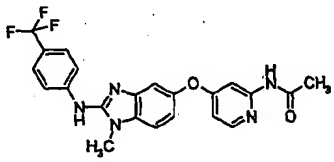
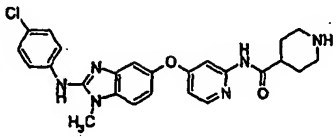
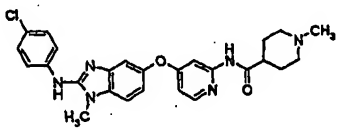
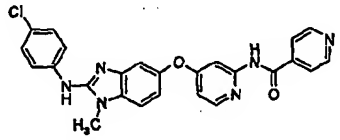
Examples 84-515

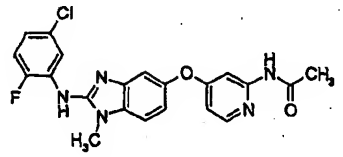
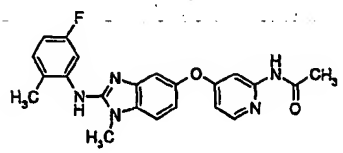
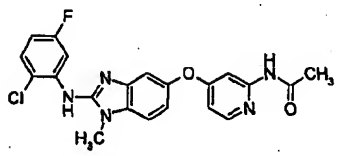
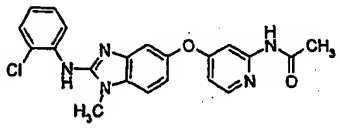
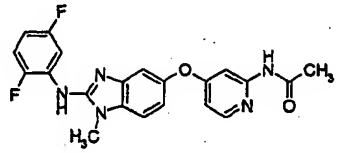
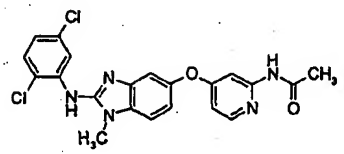
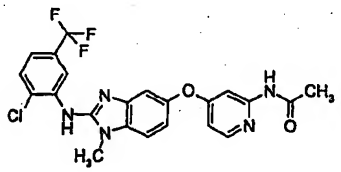
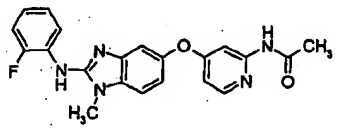
The compounds in the following Table 1 (Examples 84-515) were similarly synthesized according to the procedures described in Examples 1-83.

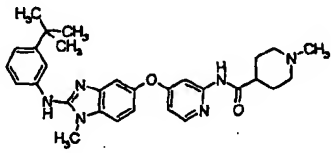
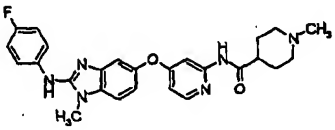
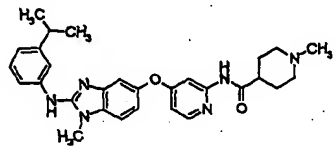
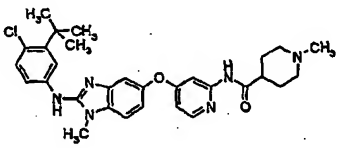
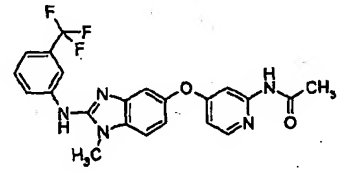
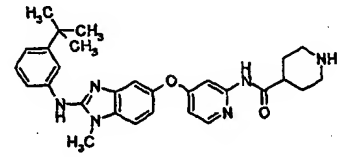
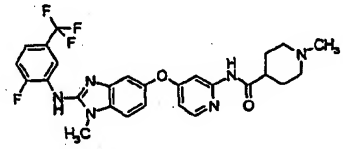
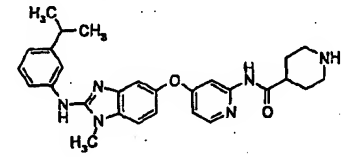
Table 1

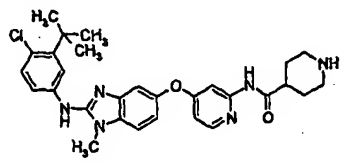
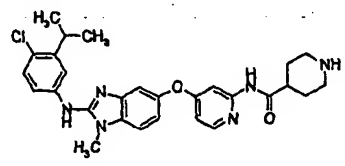
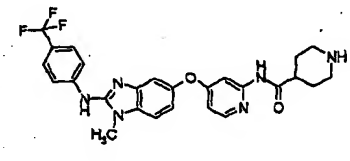
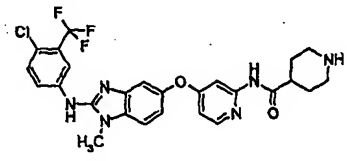
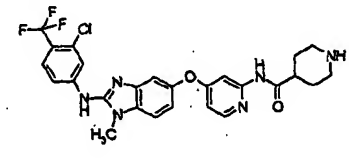
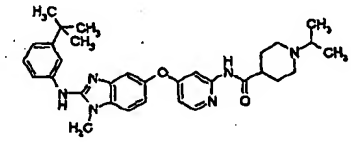
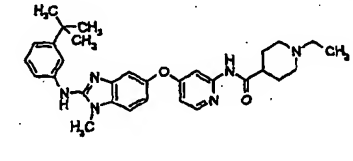
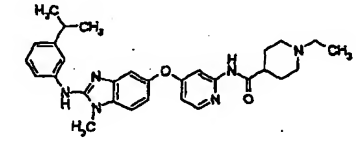
Ex.	Structure	Name	MH+
84		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	416.5
85		N-[4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	392.4
86		N-[4-({2-[(3-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5

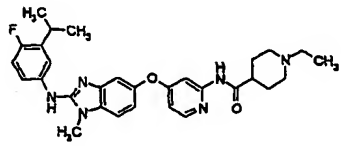
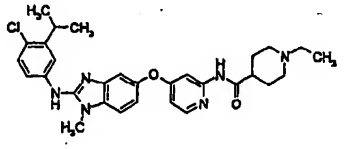
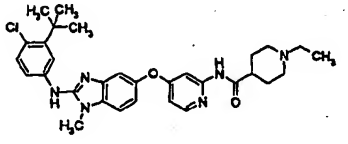
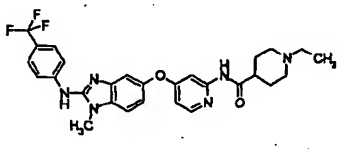
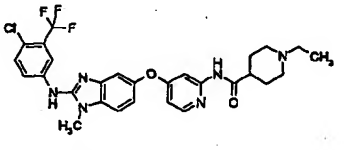
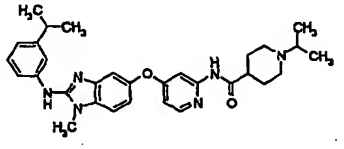
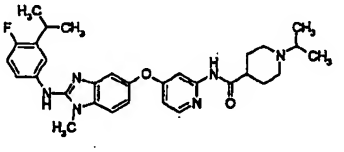
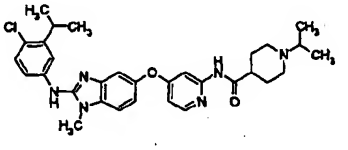
Ex.	Structure	Name	MH+
87		N-{4-[(2-{[2-fluoro-5-(trifluoro methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	460.4
88		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
89		N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	458.4
90		N-[4-({2-[(4-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	430.5
91		N-[4-({2-[(4-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	416.5
92		N-[4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	408.9
93		N-{4-[(2-{[4-chloro-3-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	476.9
94		N-[4-({2-[(4-isopropyl-3-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	430.5

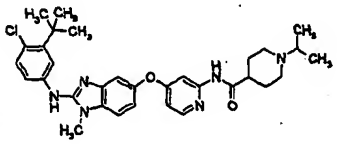
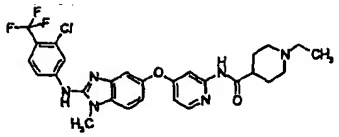
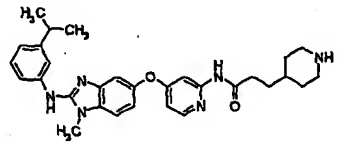
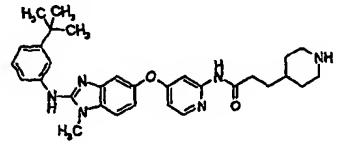
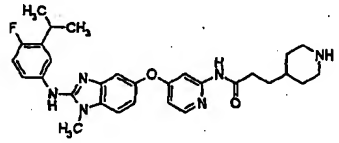
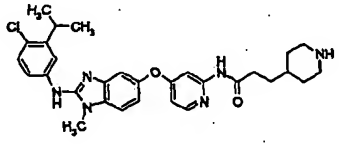
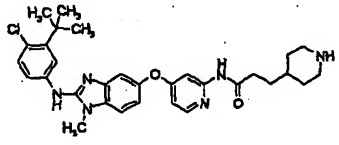
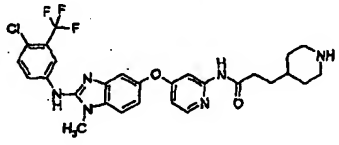
Ex.	Structure	Name	MH+
95		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	465
96		N-[4-({2-[(4-chloro-3-thien-2-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	491
97		N-[4-({2-[(4-bromo-3-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	467.3
98		N-[4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	453.3
99		N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	442.4
100		N-[4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	478
101		N-[4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide	492
102		N-[4-({2-[(4-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]isonicotinamide	471.9

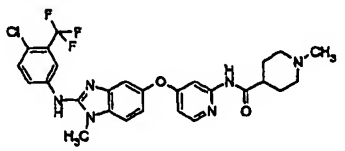
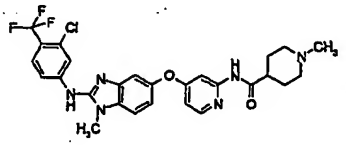
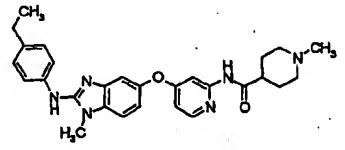
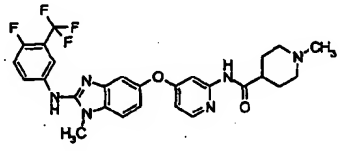
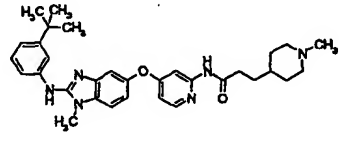
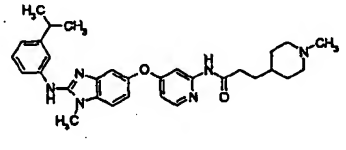
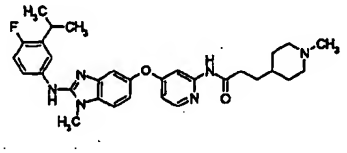
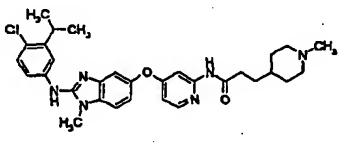
Ex.	Structure	Name	MH+
103		N-[4-({2-[(5-chloro-2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	426.8
104		N-[4-({2-[(5-fluoro-2-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	406.4
105		N-[4-({2-[(2-chloro-5-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	426.8
106		N-[4-({2-[(2-chlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]acetamide	408.9
107		N-[4-({2-[(2,5-difluorophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	410.4
108		N-[4-({2-[(2,5-dichlorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	443.3
109		N-{4-[(2-{[2-chloro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	476.9
110		N-[4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]acetamide	392.4

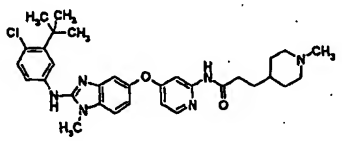
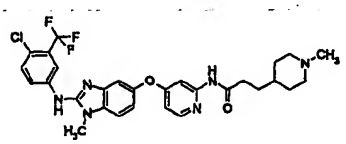
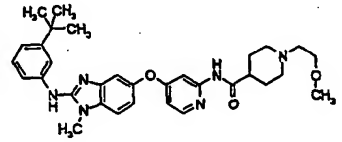
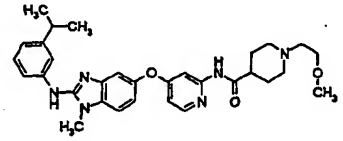
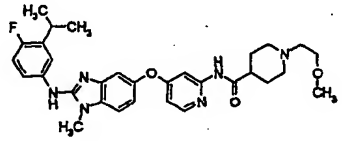
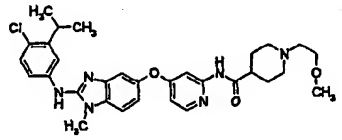
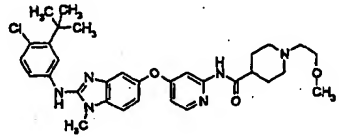
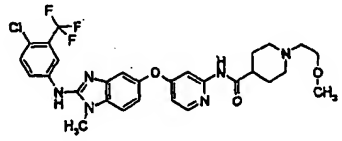
Ex.	Structure	Name	MH+
111		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methyl-piperidine-4-carboxamide	513.7
112		N-[4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]-1-methylpiperidine-4-carboxamide	475.5
113		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide	499.6
114		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide	548.1
115		N-{4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	442.4
116		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]piperidine-4-carboxamide	499.6
117		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-methylpiperidine-4-carboxamide	543.5
118		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	485.6

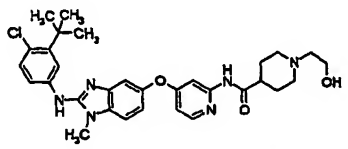
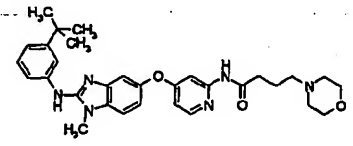
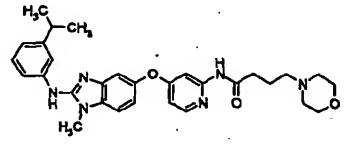
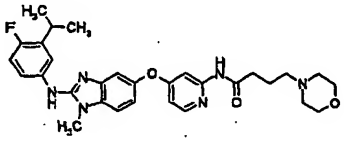
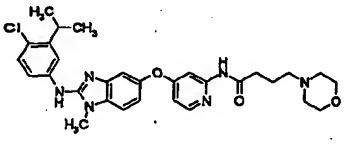
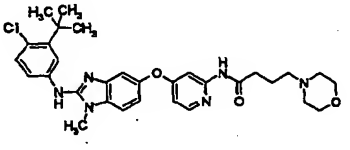
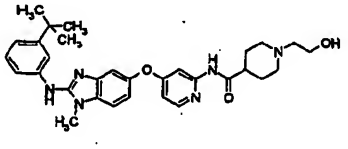
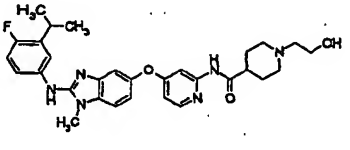
Ex.	Structure	Name	MH+
119		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	534.1
120		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	520
121		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	511.5
122		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	546
123		N-{4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	546
124		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-1-isopropyl-piperidine-4-carboxamide	541.7
125		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-ethyl-piperidine-4-carboxamide	527.7
126		1-ethyl-N-[4-({2-[(3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	513.7

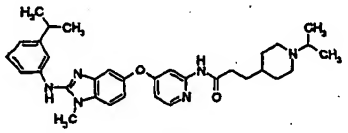
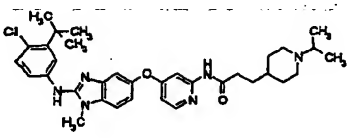
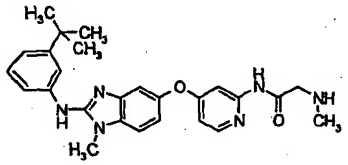
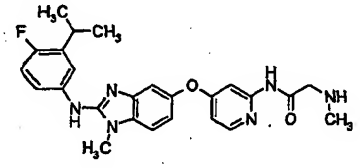
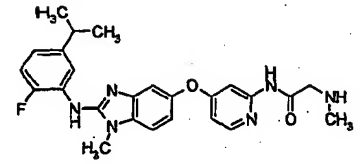
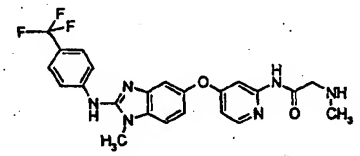
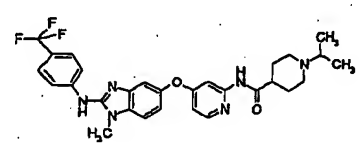
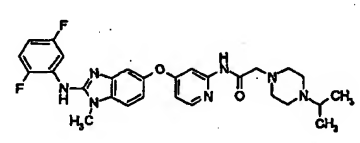
Ex.	Structure	Name	MH+
127		1-ethyl-N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	531.6
128		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-ethylpiperidine-4-carboxamide	548.1
129		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-ethylpiperidine-4-carboxamide	562.1
130		1-ethyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	539.6
131		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-ethylpiperidine-4-carboxamide	574
132		1-isopropyl-N-[4-({2-[(3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	527.7
133		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	545.7
134		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	562.1

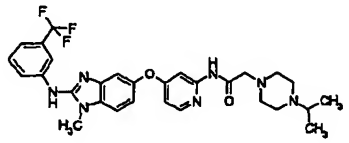
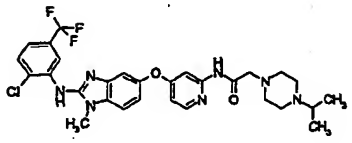
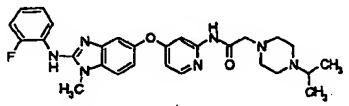
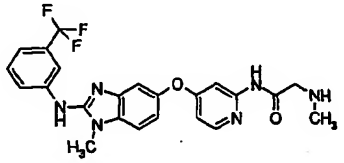
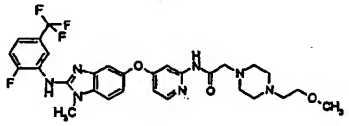
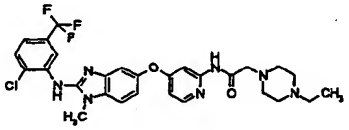
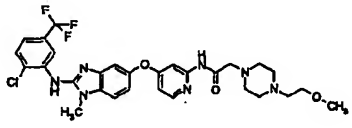
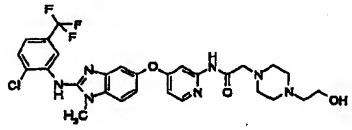
Ex.	Structure	Name	MH+
135		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	576.2
136		N-{4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-ethylpiperidine-4-carboxamide	574
137		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-piperidin-4-ylpropanamide	513.7
138		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-piperidin-4-ylpropanamide	527.7
139		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-piperidin-4-ylpropanamide	531.6
140		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-piperidin-4-ylpropanamide	548.1
141		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-piperidin-4-ylpropanamide	562.1
142		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-piperidin-4-ylpropanamide	574

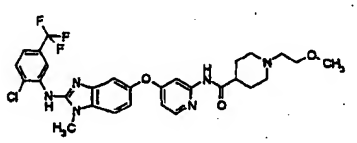
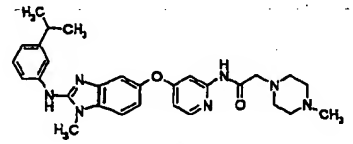
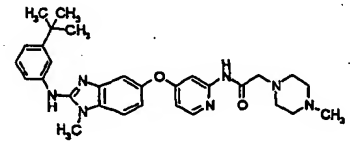
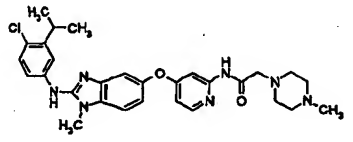
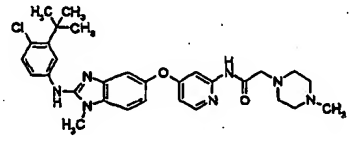
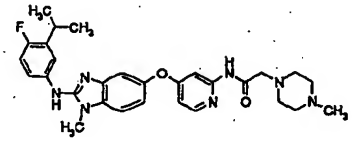
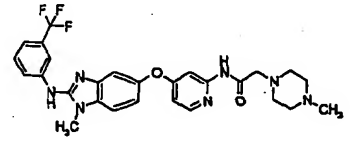
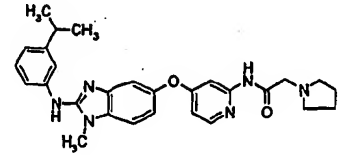
Ex.	Structure	Name	MH+
143		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-methylpiperidine-4-carboxamide	560
144		N-{4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-methylpiperidine-4-carboxamide	560
145		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]-1-methylpiperidine-4-carboxamide	485.6
146		N-{4-[(2-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-methylpiperidine-4-carboxamide	543.5
147		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-methyl-piperidin-4-yl)propanamide	541.7
148		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-methyl-piperidin-4-yl)propanamide	527.7
149		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-methylpiperidin-4-yl)propanamide	545.7
150		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-methylpiperidin-4-yl)-propanamide	562.1

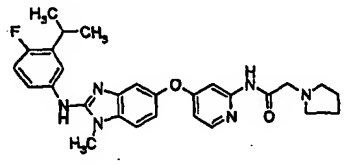
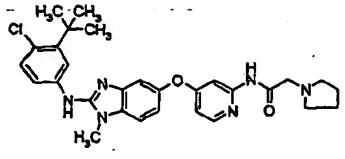
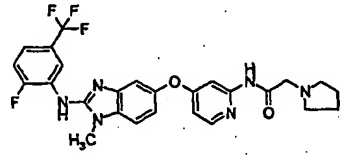
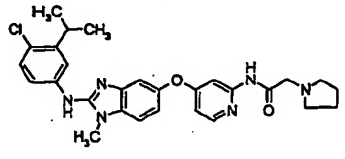
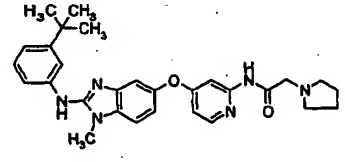
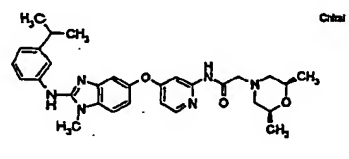
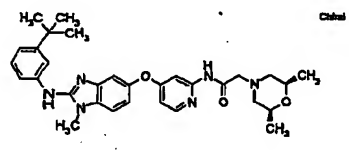
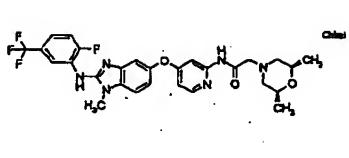
Ex.	Structure	Name	MH+
151		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-methylpiperidin-4-yl)-propanamide	576.2
152		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-3-(1-methylpiperidin-4-yl)-propanamide	588
153		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-1-(2-methoxy-ethyl)piperidine-4-carboxamide	557.7
154		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-methoxy-ethyl)piperidine-4-carboxamide	543.7
155		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-methoxyethyl)piperidine-4-carboxamide	561.7
156		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-methoxyethyl)piperidine-4-carboxamide	578.1
157		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-methoxyethyl)piperidine-4-carboxamide	592.2
158		N-{4-[(2-{[4-chloro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide	604

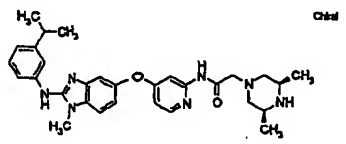
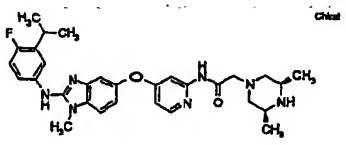
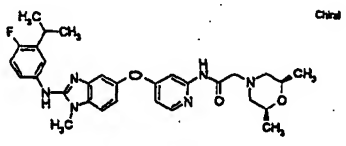
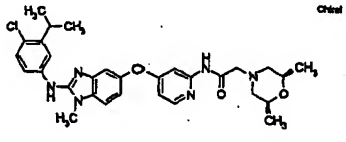
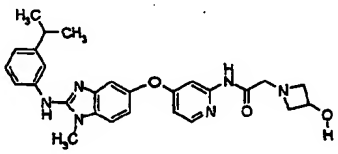
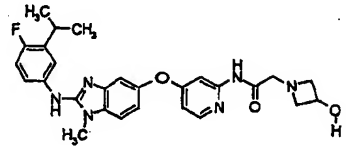
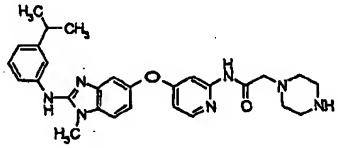
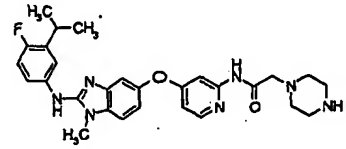
Ex.	Structure	Name	MH+
159		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-hydroxyethyl)piperidine-4-carboxamide	578.1
160		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	543.7
161		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	529.7
162		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	547.6
163		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	564.1
164		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	578.1
165		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-hydroxy-ethyl)piperidine-4-carboxamide	543.7
166		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-hydroxyethyl)piperidine-4-carboxamide	547.6

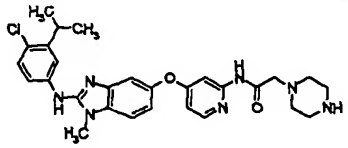
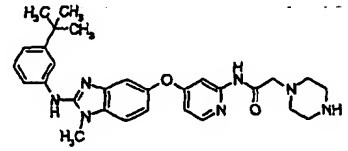
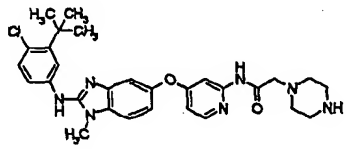
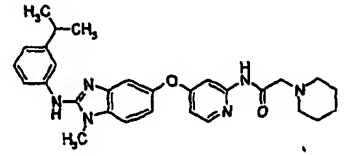
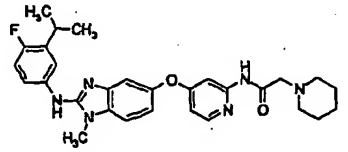
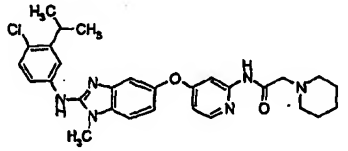
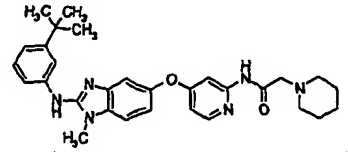
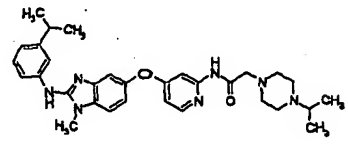
Ex.	Structure	Name	MH+
167		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-isopropyl-piperidin-4-yl)propanamide	555.7
168		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-(1-isopropylpiperidin-4-yl)-propanamide	604.2
169		N~1~-[4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-methyl-glycinamide	459.6
170		N~1~-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-methylglycinamide	463.5
171		N~1~-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~-methylglycinamide	463.5
172		N~2~-methyl-N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	471.5
173		1-isopropyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	553.6
174		N-[4-({2-[(2,5-difluorophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropyl-piperazin-1-yl)acetamide	536.6

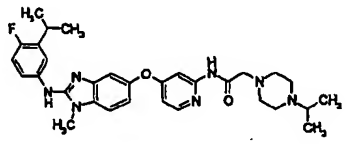
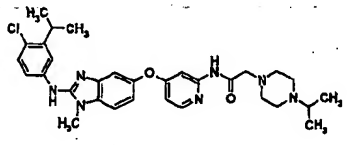
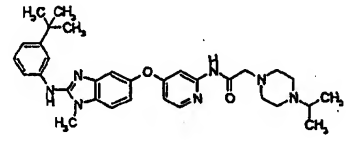
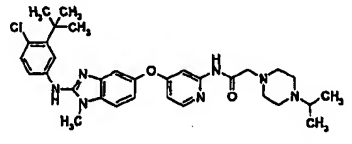
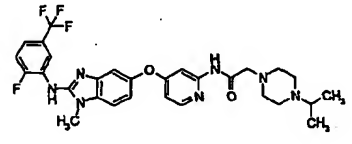
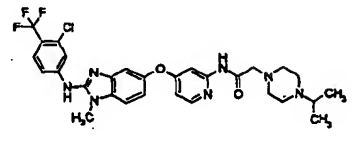
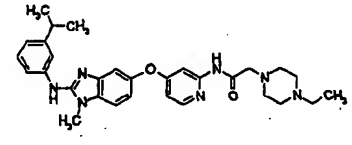
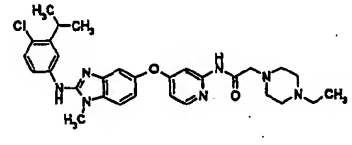
Ex.	Structure	Name	MH+
175		2-(4-isopropylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	568.6
176		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-isopropylpiperazin-1-yl)acetamide	603.1
177		N-[4-({2-[(2-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]-2-(4-isopropyl-piperazin-1-yl)acetamide	518.6
178		N~2~-methyl-N~1~-{4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	471.5
179		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide	602.6
180		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-ethylpiperazin-1-yl)acetamide	589
181		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide	619.1
182		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-hydroxyethyl)piperazin-1-yl]acetamide	605

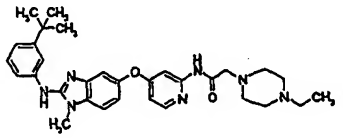
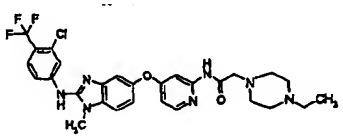
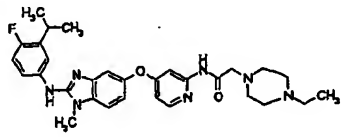
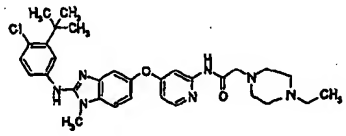
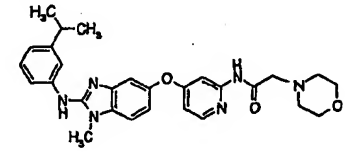
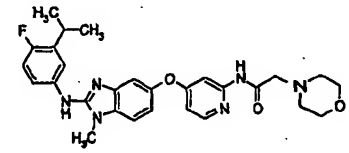
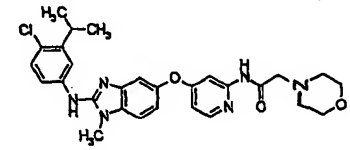
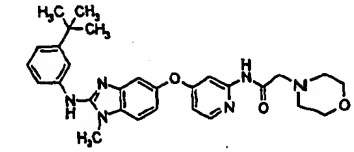
Ex.	Structure	Name	MH+
183		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-methoxyethyl)piperidine-4-carboxamide	604
184		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperazin-1-yl)acetamide	514.6
185		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methyl-piperazin-1-yl)acetamide	528.7
186		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperazin-1-yl)acetamide	549.1
187		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperazin-1-yl)acetamide	563.1
188		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperazin-1-yl)acetamide	532.6
189		2-(4-methylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	540.6
190		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	485.6

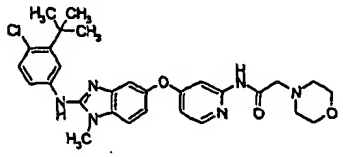
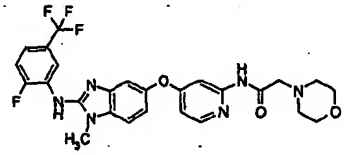
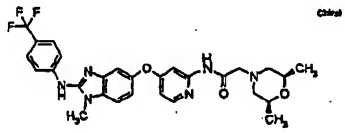
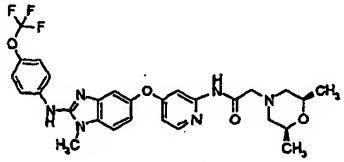
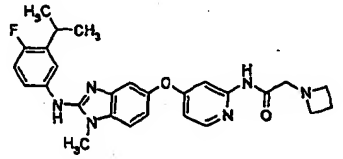
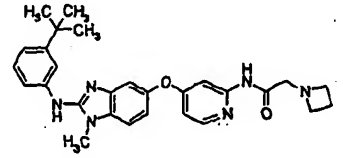
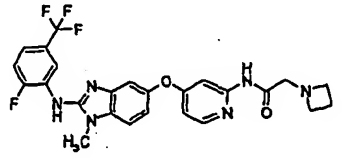
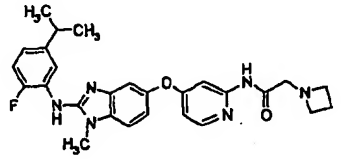
Ex.	Structure	Name	MH+
191		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	503.6
192		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	534.1
193		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-pyrrolidin-1-ylacetamide	529.5
194		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	520
195		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	499.6
196		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[4-({2-[(3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	529.7
197		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]acetamide	543.7
198		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	573.6

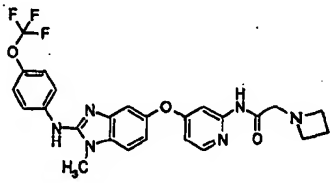
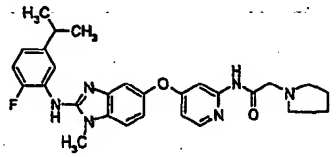
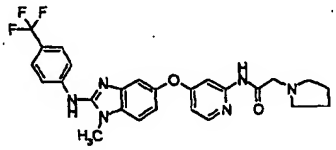
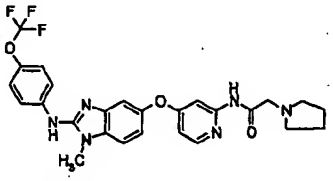
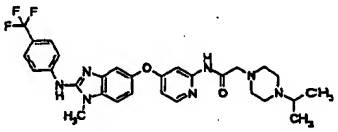
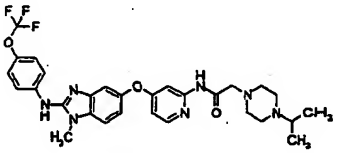
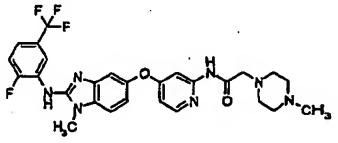
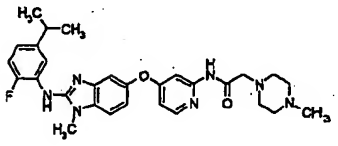
Ex.	Structure	Name	MH+
199		2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[4-({2-[(3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	528.7
200		2-[(3R,5S)-3,5-dimethylpiperazin-1-yl]-N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	546.7
201		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	547.6
202		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]acetamide	564.1
203		2-(3-hydroxyazetidin-1-yl)-N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]acetamide	487.6
204		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-hydroxyazetidin-1-yl)-acetamide	505.6
205		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperazin-1-ylacetamide	500.6
206		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperazin-1-ylacetamide	518.6

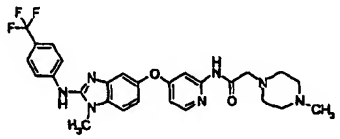
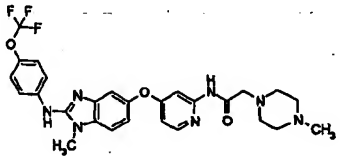
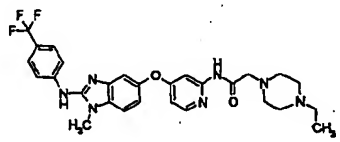
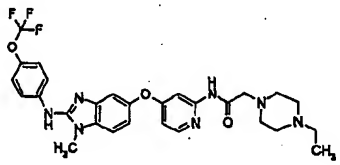
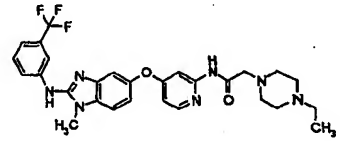
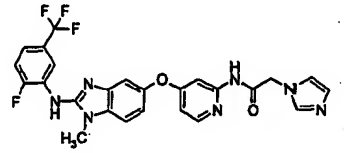
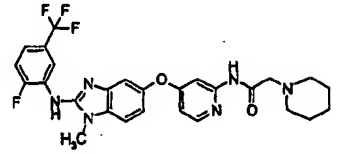
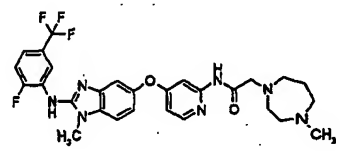
Ex.	Structure	Name	MH+
207		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperazin-1-ylacetamide	535.1
208		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-piperazin-1-ylacetamide	514.6
209		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperazin-1-ylacetamide	549.1
210		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide	499.6
211		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide	517.6
212		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide	534.1
213		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide	513.7
214		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropyl-piperazin-1-yl)acetamide	542.7

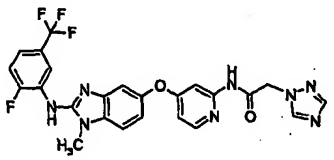
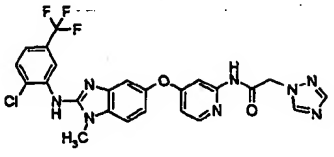
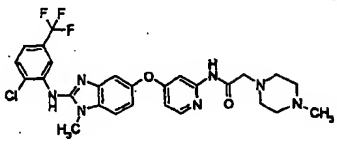
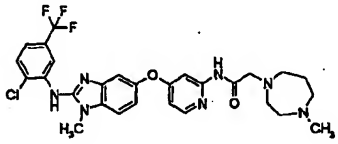
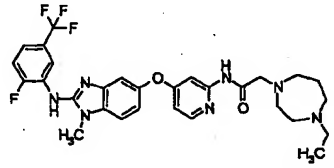
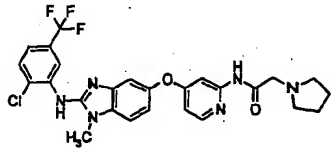
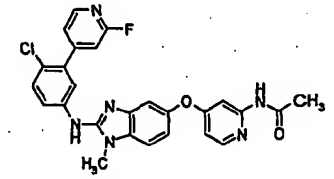
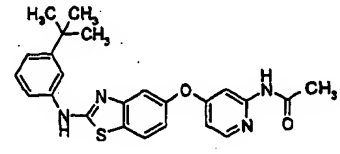
Ex.	Structure	Name	MH+
215		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)-acetamide	560.7
216		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)acetamide	577.1
217		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-(4-isopropyl-piperazin-1-yl)acetamide	556.7
218		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)-acetamide	591.2
219		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-isopropylpiperazin-1-yl)acetamide	586.6
220		N-{4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-isopropylpiperazin-1-yl)-acetamide	603.1
221		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]acetamide	528.7
222		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-ethylpiperazin-1-yl)acetamide	563.1

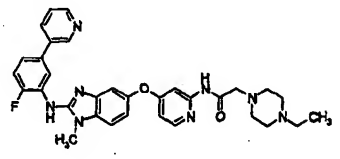
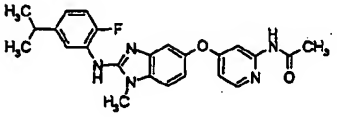
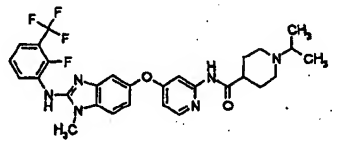
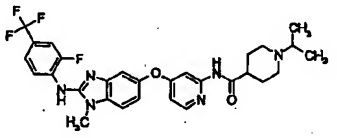
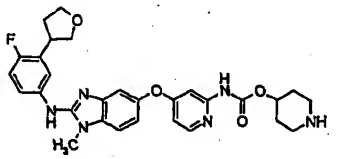
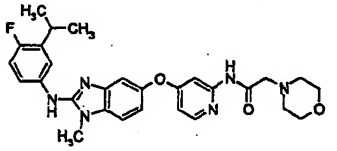
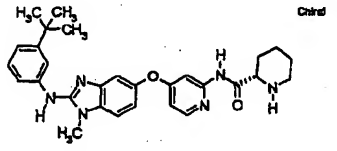
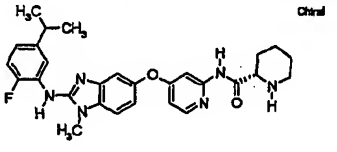
Ex.	Structure	Name	MH+
223		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-(4-ethyl-piperazin-1-yl)acetamide	542.7
224		N-{4-[(2-{[3-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-ethylpiperazin-1-yl)acetamide	589
225		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(4-fluoro-3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	546.7
226		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-ethylpiperazin-1-yl)acetamide	577.1
227		N-[4-({2-[(3-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	501.6
228		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	519.6
229		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	536
230		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	515.6

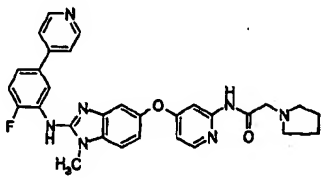
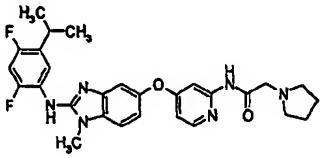
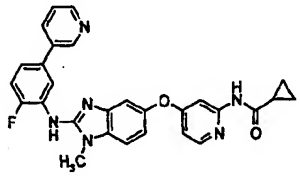
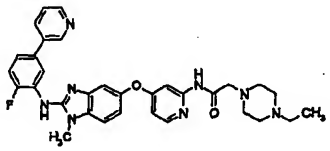
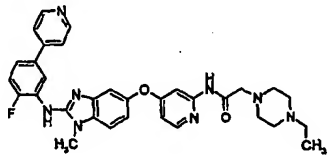
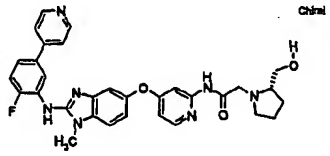
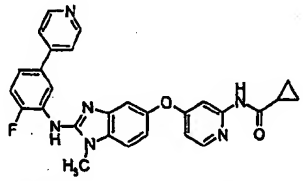
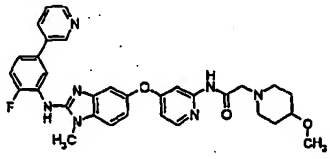
Ex.	Structure	Name	MH+
231		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	550.1
232		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-morpholin-4-ylacetamide	545.5
233		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	555.6
234		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	571.6
235		2-azetidin-1-yl-N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	489.6
236		2-azetidin-1-yl-N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	485.6
237		2-azetidin-1-yl-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	515.5
238		2-azetidin-1-yl-N-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	489.6

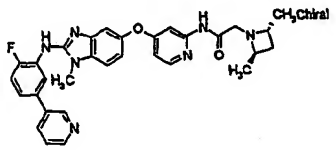
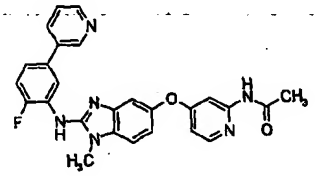
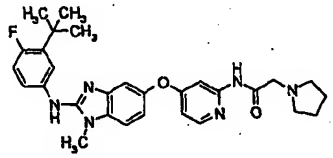
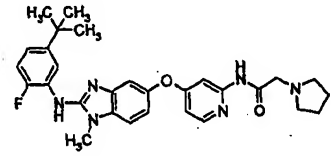
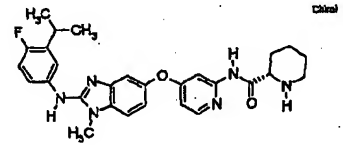
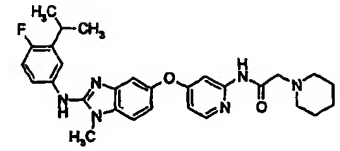
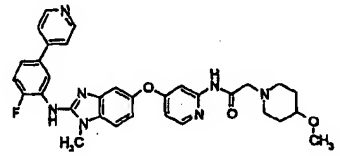
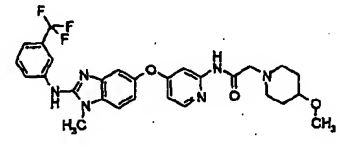
Ex.	Structure	Name	MH+
239		2-azetidin-1-yl-N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	513.5
240		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	503.6
241		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-pyrrolidin-1-ylacetamide	511.5
242		N-{4-[(1-methyl-2-{[4-(trifluoro-methoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-pyrrolidin-1-ylacetamide	527.5
243		2-(4-isopropylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	568.6
244		2-(4-isopropylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	584.6
245		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methylpiperazin-1-yl)-acetamide	558.5
246		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methylpiperazin-1-yl)-acetamide	532.6

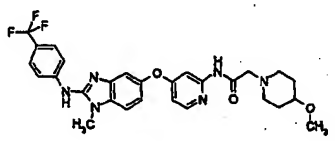
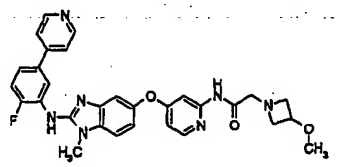
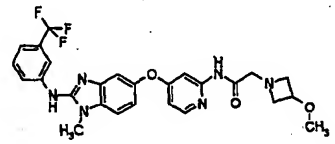
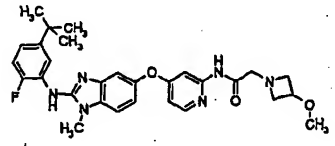
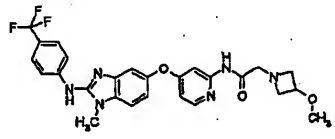
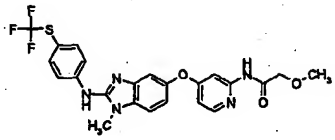
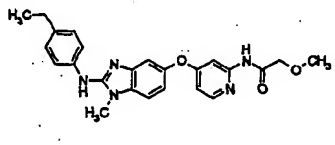
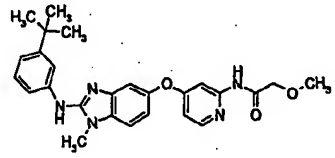
Ex.	Structure	Name	MH+
247		2-(4-methylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	540.6
248		2-(4-methylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	556.6
249		2-(4-ethylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	554.6
250		2-(4-ethylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethoxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	570.6
251		2-(4-ethylpiperazin-1-yl)-N-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	554.6
252		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(1H-imidazol-1-yl)acetamide	526.5
253		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-piperidin-1-ylacetamide	543.5
254		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methyl-1,4-diazepan-1-yl)acetamide	572.6

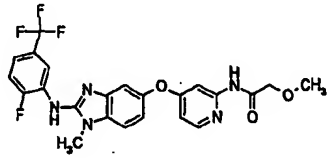
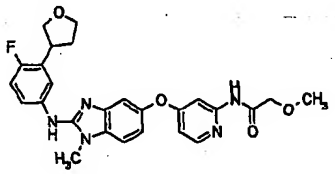
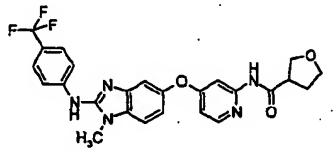
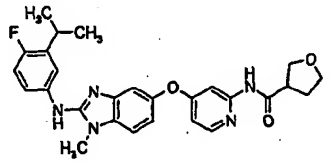
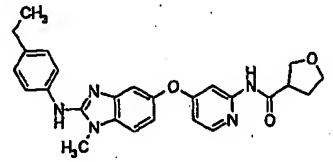
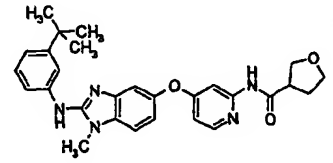
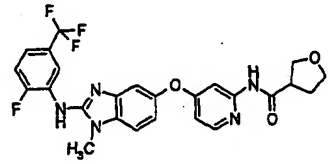
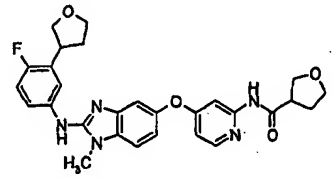
Ex.	Structure	Name	MH+
255		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(1H-1,2,4-triaziol-1-yl)acetamide	527.5
256		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(1H-1,2,4-triazol-1-yl)acetamide	543.9
257		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methylpiperazin-1-yl)-acetamide	575
258		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methyl-1,4-diazepan-1-yl)-acetamide	589
259		2-(4-ethyl-1,4-diazepan-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	586.6
260		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-pyrrolidin-1-ylacetamide	546
261		N-{4-[(2-{[4-chloro-3-(2-fluoro-pyridin-4-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	503.9
262		N-[4-({2-[(3-tert-butylphenyl)amino]-1,3-benzothiazol-5-yl}oxy)pyridin-2-yl]acetamide	433.5

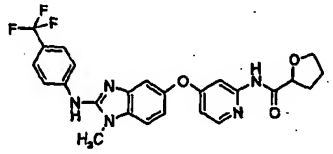
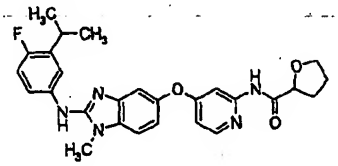
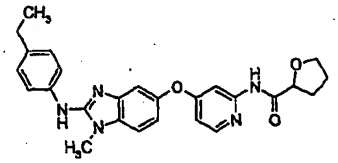
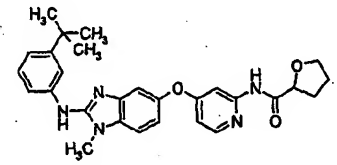
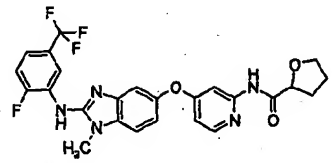
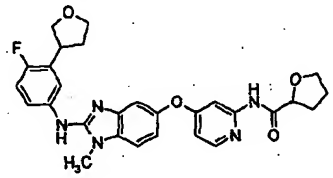
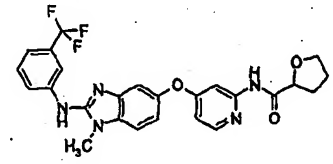
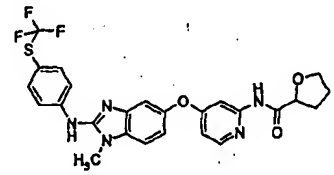
Ex.	Structure	Name	MH+
263		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(2-fluoro-5-pyridin-3-yl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	581.7
264		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	434.5
265		N-{4-[(2-{[2-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	571.6
266		N-{4-[(2-{[2-fluoro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	571.6
267		piperidin-4-yl 4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	547.6
268		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-morpholin-4-ylacetamide	519.6
269		(2S)-N-[4-({2-[(3-tert-butyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-2-carboxamide	499.6
270		(2S)-N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-2-carboxamide	503.6

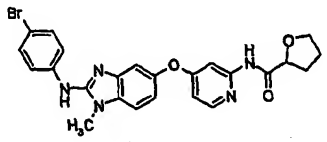
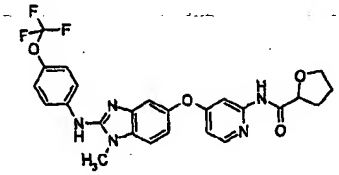
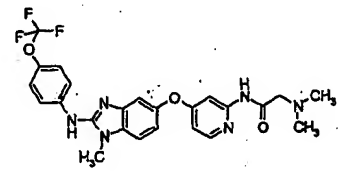
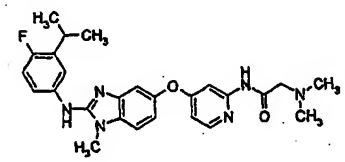
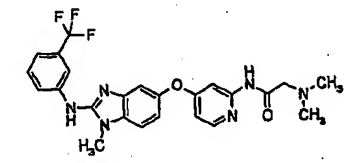
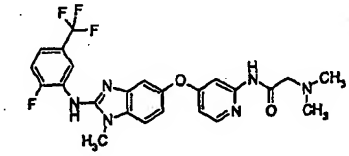
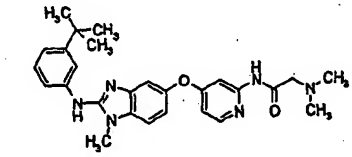
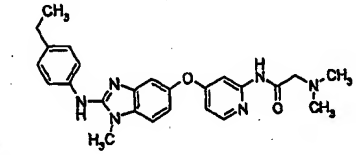
Ex.	Structure	Name	MH+
271		N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	538.6
272		N-[4-({2-[(2,4-difluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	521.6
273		N-[4-({2-[(2-fluoro-5-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]cyclopropanecarboxamide	495.5
274		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(2-fluoro-5-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	581.7
275		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	581.7
276		N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-[(2S)-2-(hydroxymethyl)pyrrolidin-1-yl]acetamide	568.6
277		N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]cyclopropanecarboxamide	495.5
278		N-[4-({2-[(2-fluoro-5-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methoxypiperidin-1-yl)acetamide	582.6

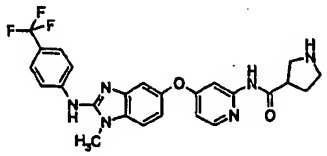
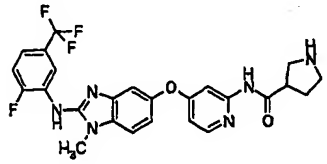
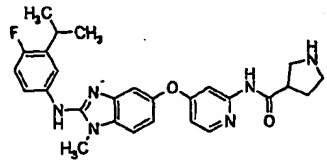
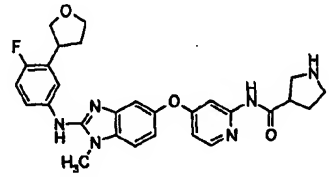
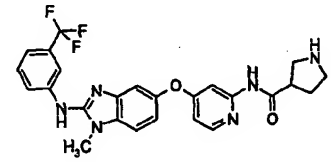
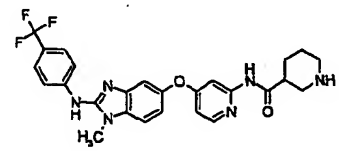
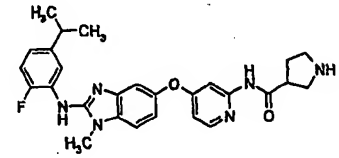
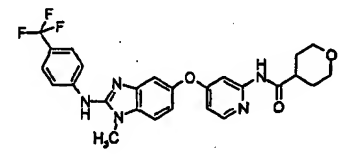
Ex.	Structure	Name	MH+
279		2-[(2R,4R)-2,4-dimethylazetidin-1-yl]-N-[4-({2-[(2-fluoro-5-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	552.6
280		N-[4-({2-[(2-fluoro-5-pyridin-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	469.5
281		N-[4-({2-[(3-tert-butyl-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	517.6
282		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-pyrrolidin-1-ylacetamide	517.6
283		(2S)-N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-2-carboxamide	503.6
284		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-piperidin-1-ylacetamide	517.6
285		N-[4-({2-[(2-fluoro-5-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methoxypiperidin-1-yl)-acetamide	582.6
286		2-(4-methoxypiperidin-1-yl)-N-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	555.6

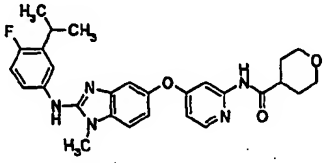
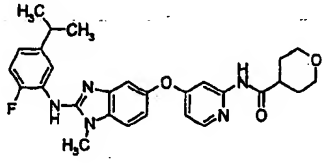
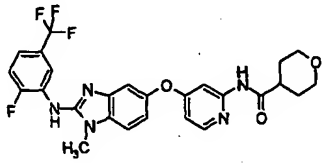
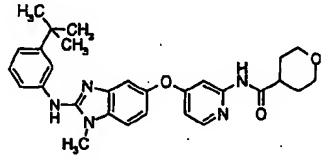
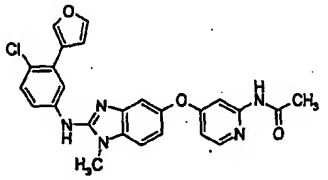
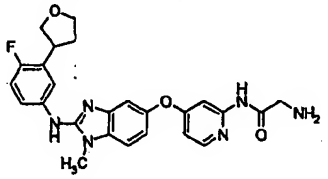
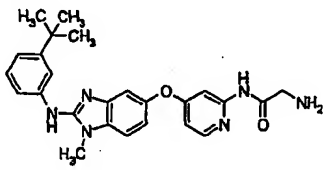
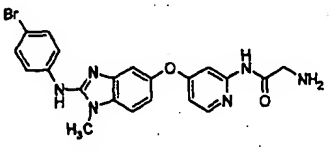
Ex.	Structure	Name	MH+
287		2-(4-methoxypiperidin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	555.6
288		N-[4-({2-[(2-fluoro-5-pyridin-4-yl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-methoxyazetidin-1-yl)-acetamide	554.6
289		2-(3-methoxyazetidin-1-yl)-N-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	527.5
290		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-methoxyazetidin-1-yl)-acetamide	533.6
291		2-(3-methoxyazetidin-1-yl)-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	527.5
292		2-methoxy-N-(4-{[1-methyl-2-({4-[(trifluoromethyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	504.5
293		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-methoxy-acetamide	432.5
294		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-methoxy-acetamide	460.5

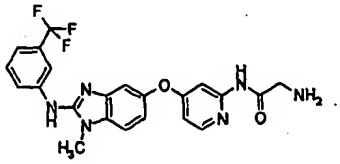
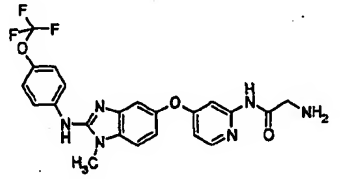
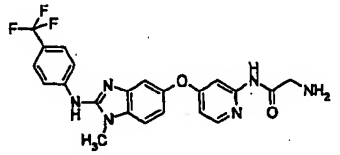
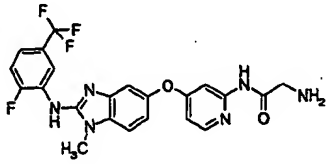
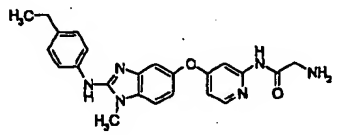
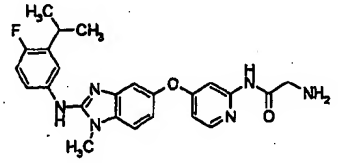
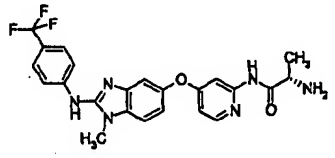
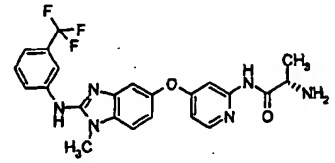
Ex.	Structure	Name	MH+
295		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-methoxyacetamide	490.4
296		N-[4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-methoxyacetamide	492.5
297		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydrofuran-3-carboxamide	498.5
298		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-tetrahydrofuran-3-carboxamide	490.5
299		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]tetrahydrofuran-3-carboxamide	458.5
300		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]tetrahydrofuran-3-carboxamide	486.6
301		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydrofuran-3-carboxamide	516.5
302		N-[4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]tetrahydrofuran-3-carboxamide	518.6

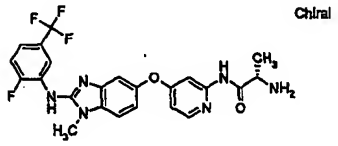
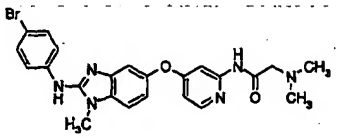
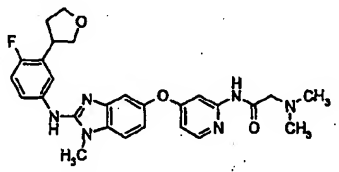
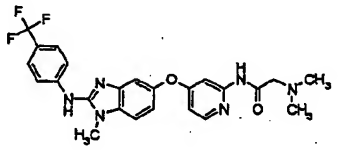
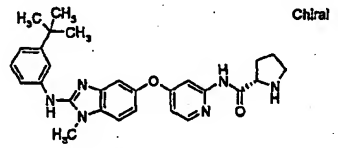
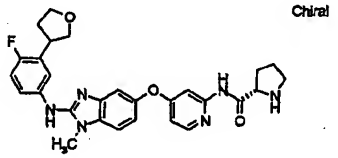
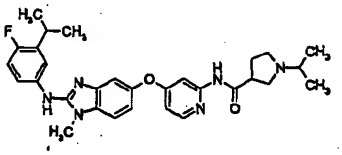
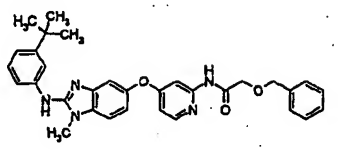
Ex.	Structure	Name	MH+
303		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydrofuran-2-carboxamide	498.5
304		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-tetrahydrofuran-2-carboxamide	490.5
305		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]tetrahydrofuran-2-carboxamide	458.5
306		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]tetrahydrofuran-2-carboxamide	486.6
307		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydrofuran-2-carboxamide	516.5
308		N-[4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]tetrahydrofuran-2-carboxamide	518.6
309		N-{4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl-tetrahydrofuran-2-carboxamide	498.5
310		N-(4-{[1-methyl-2-({4-[(trifluoro-methyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)tetrahydrofuran-2-carboxamide	530.5

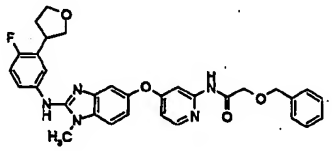
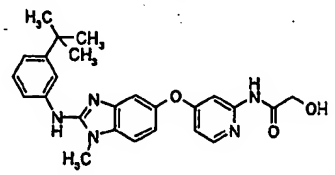
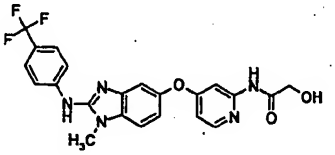
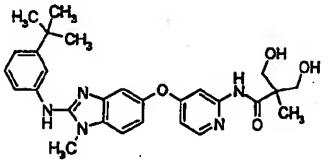
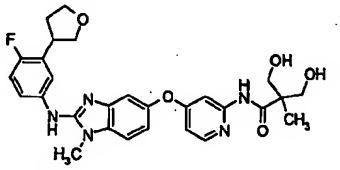
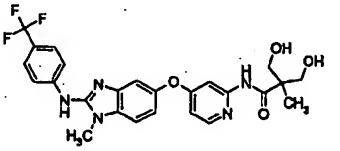
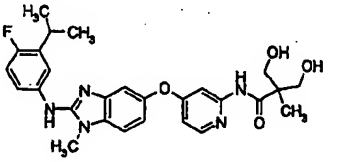
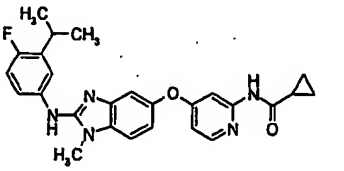
Ex.	Structure	Name	MH+
311		N-[4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)-pyridin-2-yl]tetrahydrofuran-2-carboxamide	509.4
312		N-{4-[(1-methyl-2-{[4-(trifluoro-methoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydrofuran-2-carboxamide	514.5
313		N~2~,N~2~-dimethyl-N~1~-{4-[(1-methyl-2-{[4-(trifluoromethoxy)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	501.5
314		N~1~-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	477.6
315		N~2~,N~2~-dimethyl-N~1~-{4-[(1-methyl-2-{[3-(trifluoromethyl)-phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	485.5
316		N~1~-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-N~2~,N~2~-dimethylglycinamide	503.5
317		N~1~-[4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	473.6
318		N~1~-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	445.5

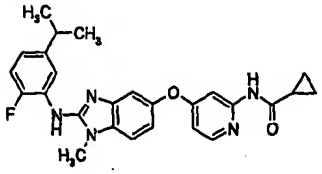
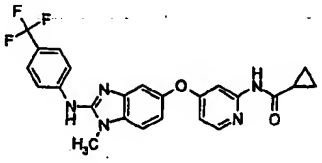
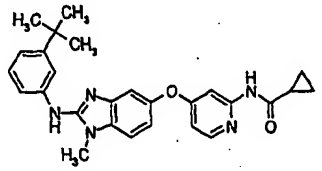
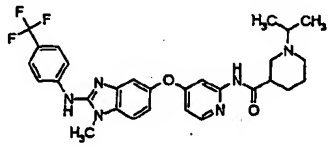
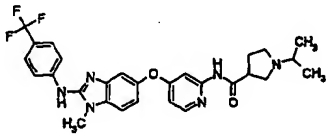
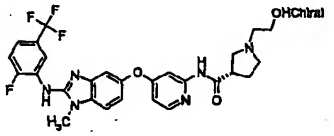
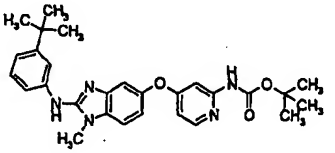
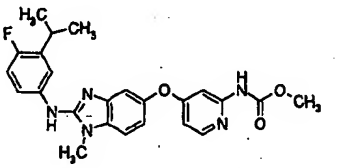
Ex.	Structure	Name	MH+
319		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-pyrrolidine-3-carboxamide	497.5
320		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-pyrrolidine-3-carboxamide	515.5
321		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-pyrrolidine-3-carboxamide	489.6
322		N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]pyrrolidine-3-carboxamide	517.6
323		N-{4-[(1-methyl-2-{[3-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-pyrrolidine-3-carboxamide	497.5
324		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-piperidine-3-carboxamide	511.5
325		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-pyrrolidine-3-carboxamide	489.6
326		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydro-2H-pyran-4-carboxamide	512.5

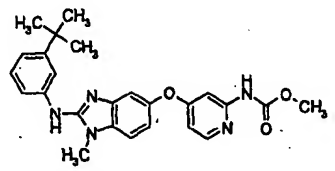
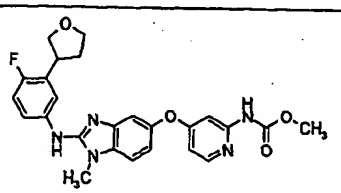
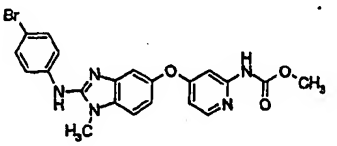
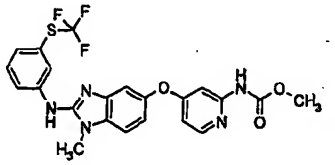
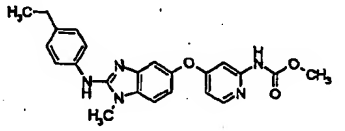
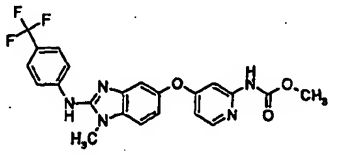
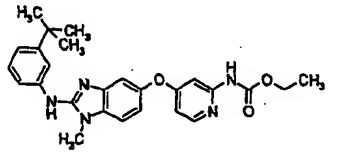
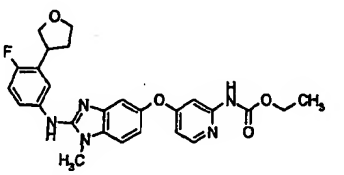
Ex.	Structure	Name	MH+
327		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-tetrahydro-2H-pyran-4-carboxamide	504.6
328		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-tetrahydro-2H-pyran-4-carboxamide	504.6
329		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-tetrahydro-2H-pyran-4-carboxamide	530.5
330		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]tetrahydro-2H-pyran-4-carboxamide	500.6
331		N-{4-[(2-{[4-chloro-3-(3-furyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	474.9
332		N~1~-[4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide	477.5
333		N~1~-[4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide	445.5
334		N~1~-[4-({2-[(4-bromophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]glycinamide	468.3

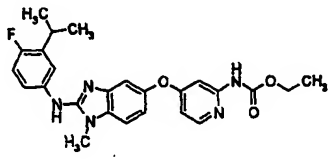
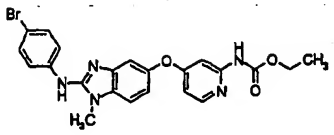
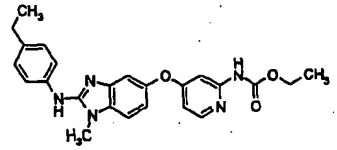
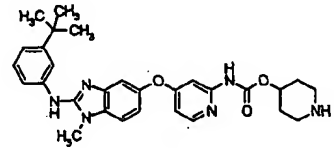
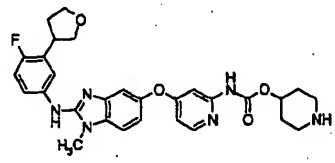
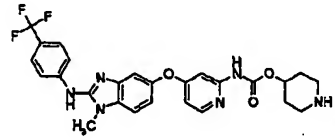
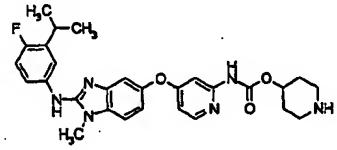
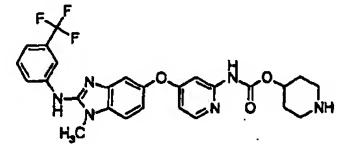
Ex.	Structure	Name	MH+
335		N~1~-{4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	457.4
336		N~1~-{4-[(1-methyl-2-{[4-(trifluoromethoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-glycinamide	473.4
337		N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-glycinamide	457.4
338		N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-glycinamide	475.4
339		N~1~-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]glycinamide	417.5
340		N~1~-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-glycinamide	449.5
341		N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-L-alaninamide	471.5
342		N~1~-{4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-L-alaninamide	471.5

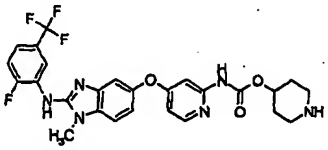
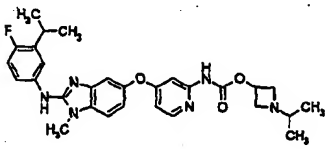
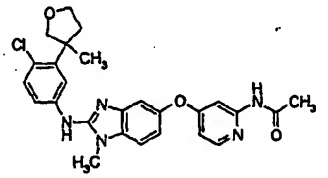
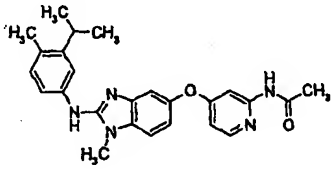
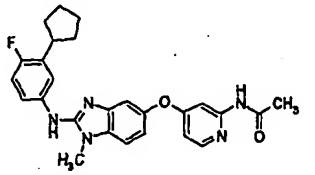
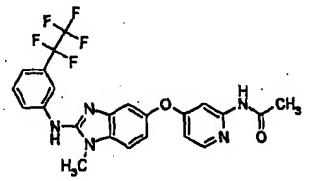
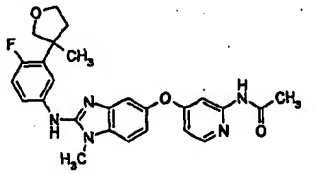
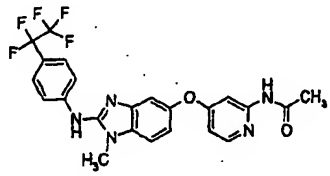
Ex.	Structure	Name	MH+
343	 Chiral	N~1~-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-L-alaninamide	489.4
344		N~1~-[4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	496.4
345		N~1~-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	505.6
346		N~2~,N~2~-dimethyl-N~1~-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}glycinamide	485.5
347	 Chiral	N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-L-prolinamide	485.6
348	 Chiral	N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-L-prolinamide	517.6
349		N-[4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpyrrolidine-3-carboxamide	531.6
350		2-(benzyloxy)-N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	536.6

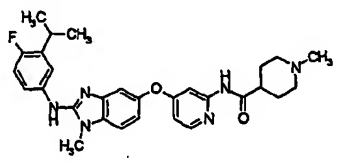
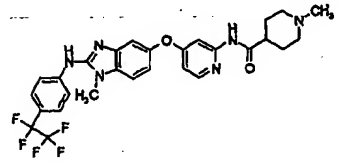
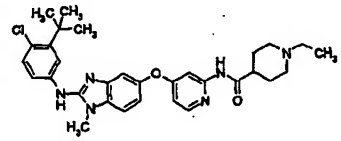
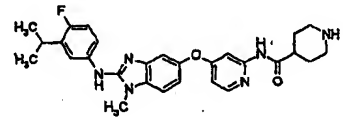
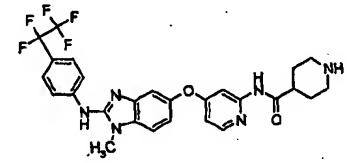
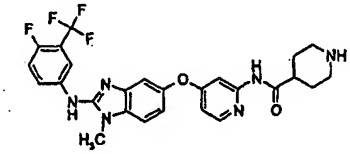
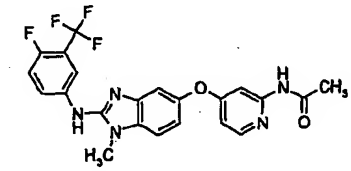
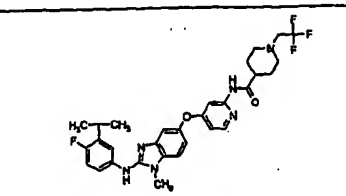
Ex.	Structure	Name	MH+
351		2-(benzyloxy)-N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	568.6
352		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-hydroxyacetamide	446.5
353		2-hydroxy-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	458.4
354		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-hydroxy-2-(hydroxymethyl)-2-methyl-propanamide	504.6
355		N-[4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-3-hydroxy-2-(hydroxymethyl)-2-methyl-propanamide	536.6
356		3-hydroxy-2-(hydroxymethyl)-2-methyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-propanamide	516.5
357		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-3-hydroxy-2-(hydroxymethyl)-2-methylpropanamide	508.6
358		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-cyclopropanecarboxamide	460.5

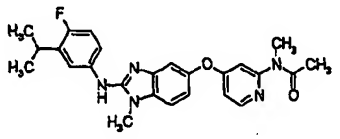
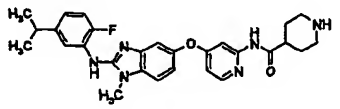
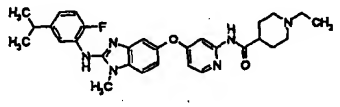
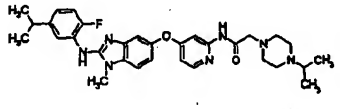
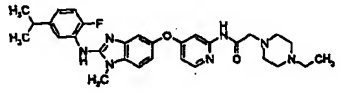
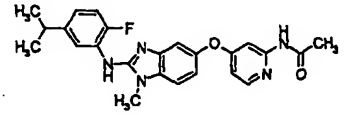
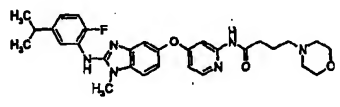
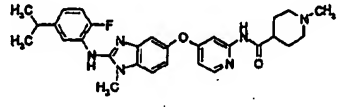
Ex.	Structure	Name	MH+
359		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-cyclopropanecarboxamide	460. 5
360		N-{4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-cyclopropanecarboxamide	468.4
361		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]cyclopropane-carboxamide	456.6
362		1-isopropyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-3-carboxamide	553.6
363		1-isopropyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}pyrrolidine-3-carboxamide	539.6
364		(3S)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-(2-hydroxy-ethyl)pyrrolidine-3-carboxamide	559.5
365		tert-butyl 4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	488.6
366		methyl 4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl-carbamate	450.5

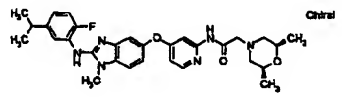
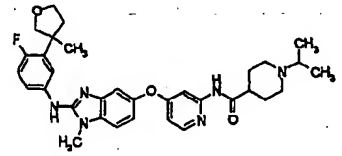
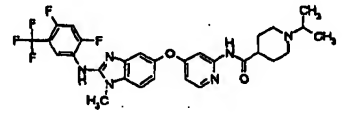
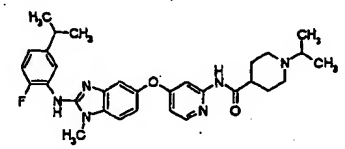
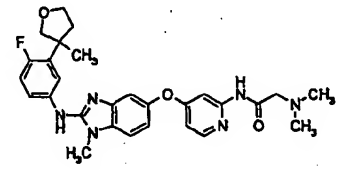
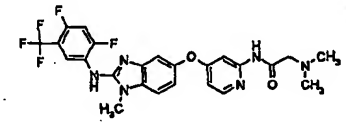
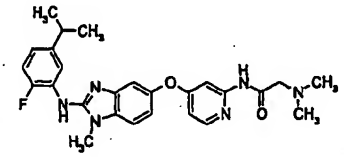
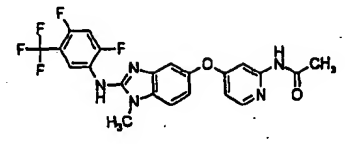
Ex.	Structure	Name	MH+
367		methyl 4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	446.5
368		methyl 4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	478.5
369		methyl 4-({2-[(4-bromophenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	469.3
370		methyl 4-{[1-methyl-2-({3-[(trifluoro-methyl)thio]phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl-carbamate	490.5
371		methyl 4-({2-[(4-ethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	418.5
372		methyl 4-[(1-methyl-2-{[4-(trifluoro-methyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl-carbamate	458.4
373		ethyl 4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	460.5
374		ethyl 4-({2-[(4-fluoro-3-tetrahydro-furan-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	492.5

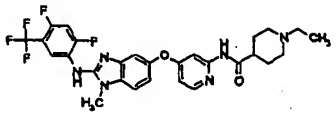
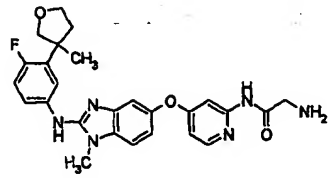
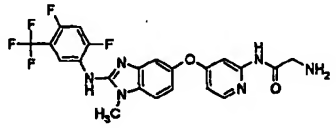
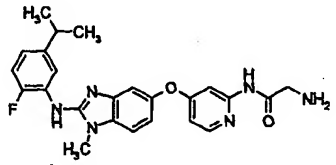
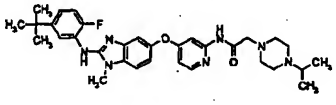
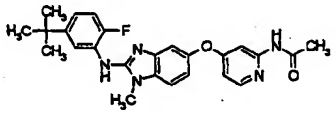
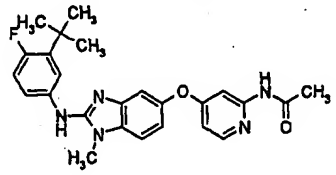
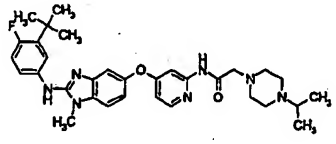
Ex.	Structure	Name	MH+
375		ethyl 4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl-carbamate	464.5
376		ethyl 4-({2-[(4-bromophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-ylcarbamate	483.3
377		ethyl 4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-ylcarbamate	432.5
378		piperidin-4-yl 4-({2-[(3-tert-butyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl-carbamate	515.6
379		piperidin-4-yl 4-({2-[(4-fluoro-3-tetrahydrofuran-3-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-ylcarbamate	547.6
380		piperidin-4-yl 4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-ylcarbamate	527.5
381		piperidin-4-yl 4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-ylcarbamate	519.6
382		piperidin-4-yl 4-[(1-methyl-2-{[3-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-ylcarbamate	527.5

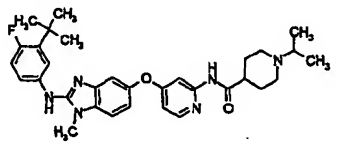
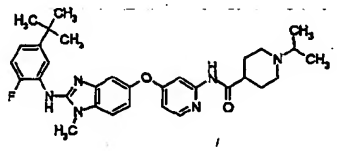
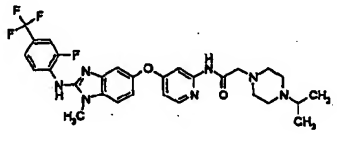
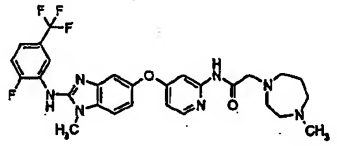
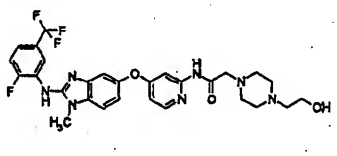
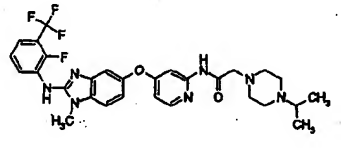
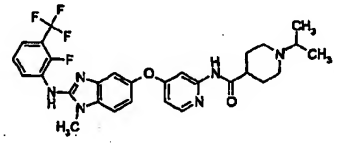
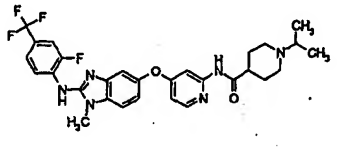
Ex.	Structure	Name	MH+
383		piperidin-4-yl 4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-ylcarbamate	545.5
384		1-isopropylazetidin-3-yl 4-({2-[(4-fluoro-3-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-ylcarbamate	533.6
385		N-{4-[(2-{[4-chloro-3-(3-methyl-tetrahydrofuran-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	493
386		N-[4-({2-[(3-isopropyl-4-methyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	430.5
387		N-[4-({2-[(3-cyclopentyl-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	460.5
388		N-{4-[(1-methyl-2-{[3-(pentafluoro-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	492.4
389		N-{4-[(2-{[4-fluoro-3-(3-methyl-tetrahydrofuran-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	476.5
390		N-{4-[(1-methyl-2-{[4-(pentafluoro-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	492.4

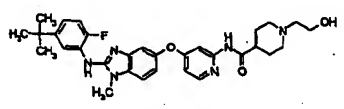
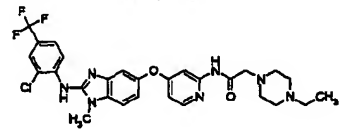
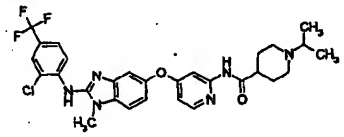
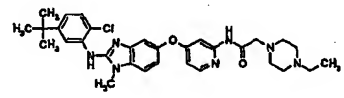
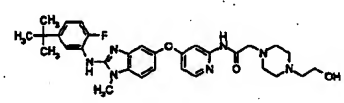
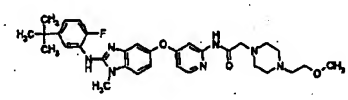
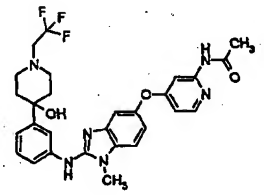
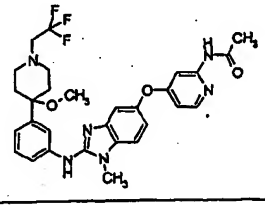
Ex.	Structure	Name	MH+
391		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide	517.6
392		1-methyl-N-{4-[(1-methyl-2-{[4-(pentafluoroethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}piperidine-4-carboxamide	575.6
393		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-ethylpiperidine-4-carboxamide	562.1
394		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-piperidine-4-carboxamide	503.6
395		N-{4-[(1-methyl-2-{[4-(pentafluoro-ethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-piperidine-4-carboxamide	561.5
396		N-{4-[(2-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-piperidine-4-carboxamide	529.5
397		N-{4-[(2-{[4-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	460.4
398		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2,2,2-trifluoroethyl)piperidine-4-carboxamide	585.6

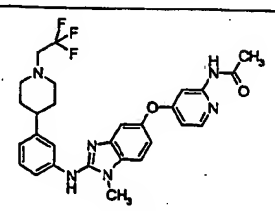
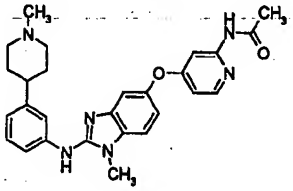
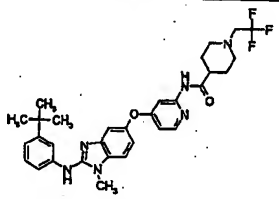
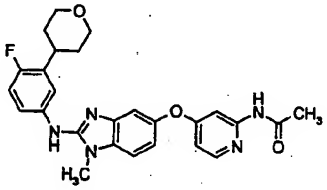
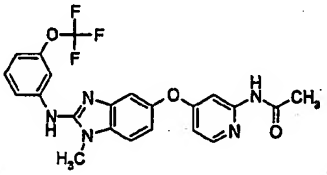
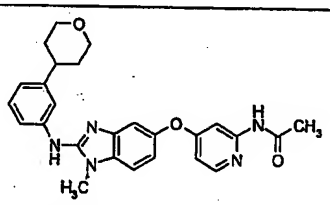
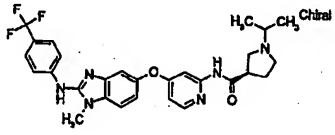
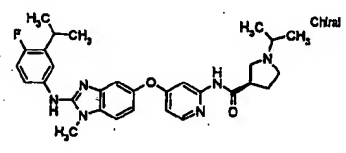
Ex.	Structure	Name	MH+
399		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N-methylacetamide	448.5
400		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-piperidine-4-carboxamide	503.6
401		1-ethyl-N-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]piperidine-4-carboxamide	531.6
402		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)-acetamide	560.7
403		2-(4-ethylpiperazin-1-yl)-N-[4-({2-[(2-fluoro-5-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	546.7
404		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	434.5
405		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-morpholin-4-ylbutanamide	547.6
406		N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-methylpiperidine-4-carboxamide	517.6

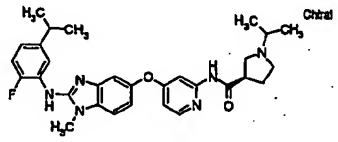
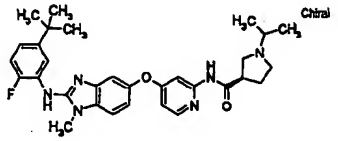
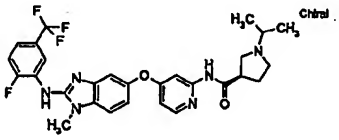
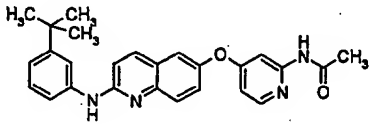
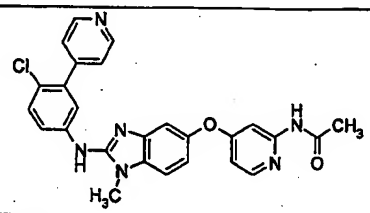
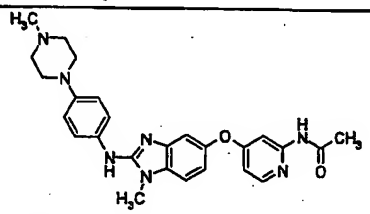
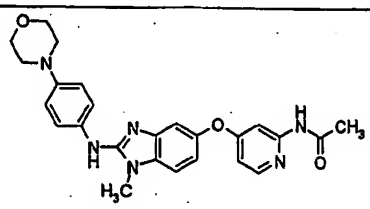
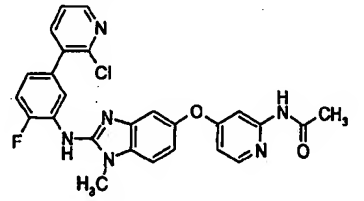
Ex.	Structure	Name	MH+
407		2-[(2R,6S)-2,6-dimethylmorpholin-4-yl]-N-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	547.6
408		N-{4-[(2-{[4-fluoro-3-(3-methyltetrahydrofuran-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	587.7
409		N-{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	589.6
410		N-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	545.7
411		N~1~-{4-[(2-{[4-fluoro-3-(3-methyltetrahydrofuran-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}-N~2~,N~2~-dimethylglycinamide	519.6
412		N~1~-{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}-N~2~,N~2~-dimethylglycinamide	521.5
413		N~1~-[4-({2-[(2-fluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-N~2~,N~2~-dimethylglycinamide	477.6
414		N-{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	478.4

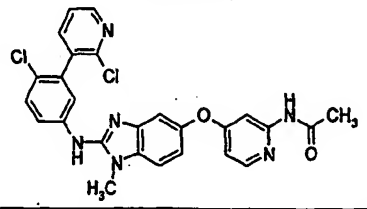
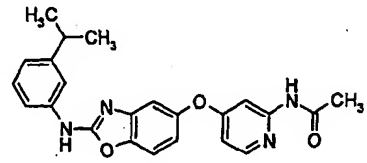
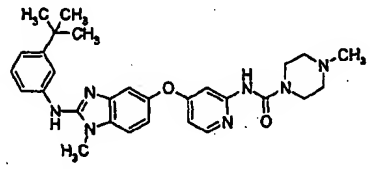
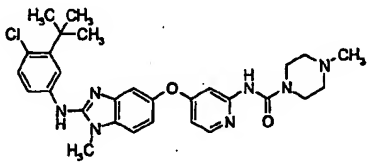
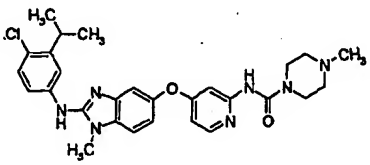
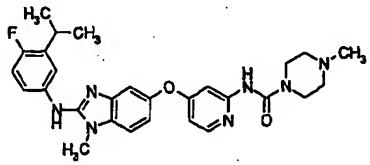
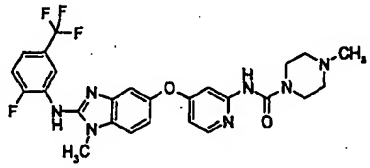
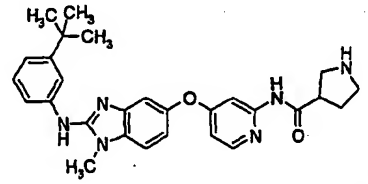
Ex.	Structure	Name	MH+
415		N-{4-[(2-{[2,4-difluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-ethylpiperidine-4-carboxamide	575.6
416		N~1~-{4-[(2-{[4-fluoro-3-(3-methyl-tetrahydrofuran-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}glycinamide	491.5
417		N~1~-{4-[(2-{[2,4-difluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}glycinamide	493.4
418		N~1~-{4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-glycinamide	449.5
419		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)-acetamide	574.7
420		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	448.5
421		N-[4-({2-[(3-tert-butyl-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	448.5
422		N-[4-({2-[(3-tert-butyl-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-isopropylpiperazin-1-yl)-acetamide	574.7

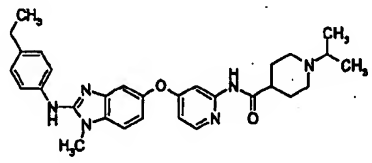
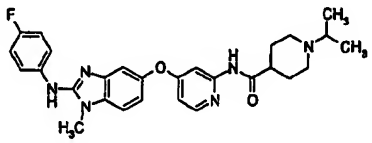
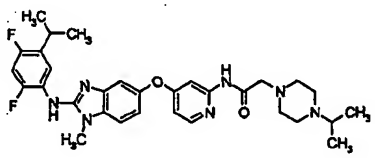
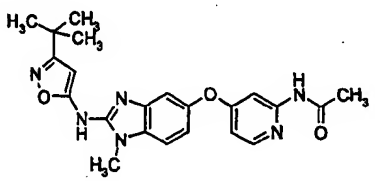
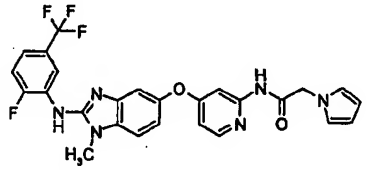
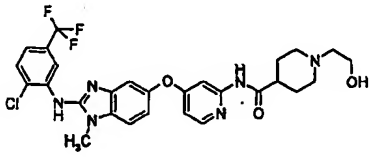
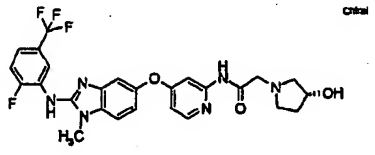
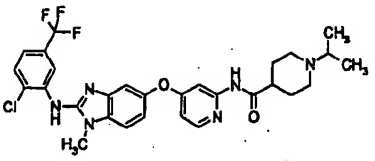
Ex.	Structure	Name	MH+
423		N-[4-({2-[(3-tert-butyl-4-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	559.7
424		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpiperidine-4-carboxamide	559.7
425		N-{4-[(2-{[2-fluoro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-isopropylpiperazin-1-yl)-acetamide	586.6
426		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-methyl-1,4-diazepan-1-yl)-acetamide	572.6
427		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-[4-(2-hydroxyethyl)piperazin-1-yl]acetamide	588.6
428		N-{4-[(2-{[2-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-isopropylpiperazin-1-yl)-acetamide	586.6
429		N-{4-[(2-{[2-fluoro-3-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	571.6
430		N-{4-[(2-{[2-fluoro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	571.6

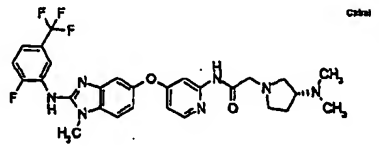
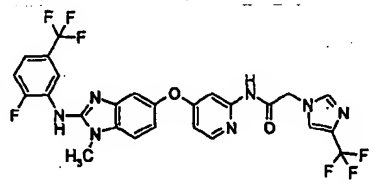
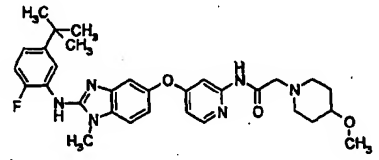
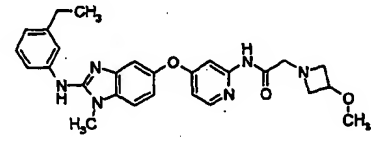
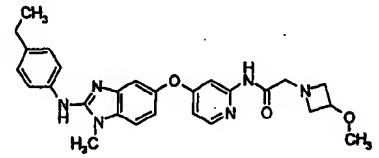
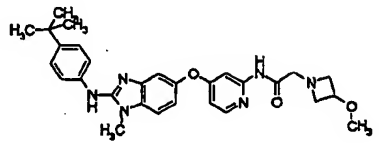
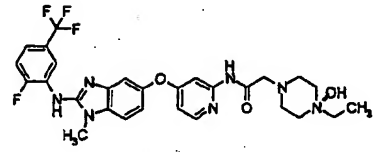
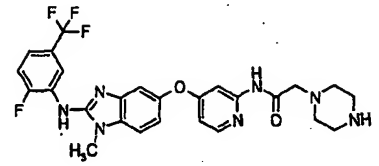
Ex.	Structure	Name	MH+
431		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-(2-hydroxyethyl)piperidine-4-carboxamide	561.7
432		N-{4-[(2-{[2-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-2-(4-ethylpiperazin-1-yl)acetamide	589
433		N-{4-[(2-{[2-chloro-4-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpiperidine-4-carboxamide	588
434		N-[4-({2-[(5-tert-butyl-2-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-ethylpiperazin-1-yl)acetamide	577.1
435		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-[4-(2-hydroxyethyl)piperazin-1-yl]acetamide	576.7
436		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-[4-(2-methoxyethyl)piperazin-1-yl]acetamide	590.7
437		N-(4-{[2-({3-[4-hydroxy-1-(2,2,2-trifluoroethyl)piperidin-4-yl]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)-acetamide	555.5
438		N-(4-{[2-({3-[4-methoxy-1-(2,2,2-trifluoroethyl)piperidin-4-yl]-phenyl}amino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)-acetamide	569.5

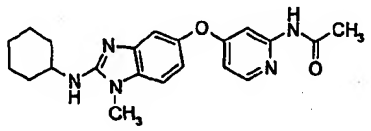
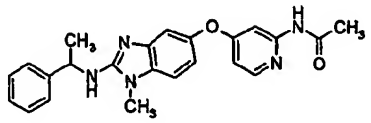
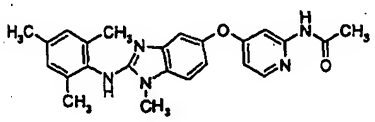
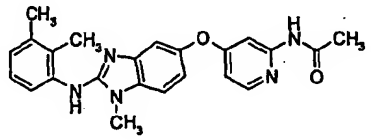
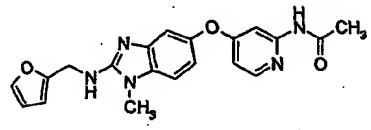
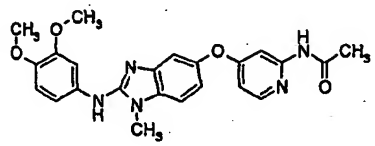
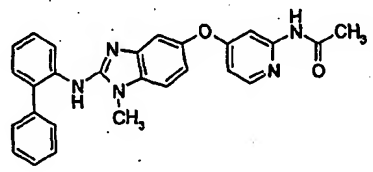
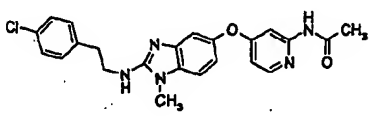
Ex.	Structure	Name	MH+
439		N-(4-{[1-methyl-2-({3-[1-(2,2,2-trifluoroethyl)piperidin-4-yl]-phenyl}amino)-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	539.6
440		N-{4-[(1-methyl-2-{[3-(1-methyl-piperidin-4-yl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	471.6
441		N-[4-({2-[(3-tert-butylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-1-(2,2,2-trifluoro-ethyl)piperidine-4-carboxamide	581.7
442		N-[4-({2-[(4-fluoro-3-tetrahydro-2H-pyran-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	476.3
443		N-{4-[(1-methyl-2-{[3-(trifluoro-methoxy)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-acetamide	458.3
444		N-[4-({1-methyl-2-[(3-tetrahydro-2H-pyran-4-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-acetamide	458.3
445		(3R)-1-isopropyl-N-{4-[(1-methyl-2-{[4-(trifluoromethyl)phenyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}pyrrolidine-3-carboxamide	359.6
446		(3R)-N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpyrrolidine-3-carboxamide	531.2

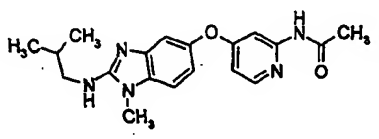
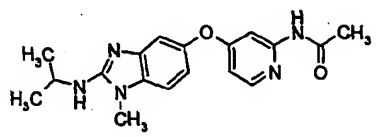
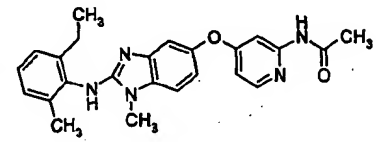
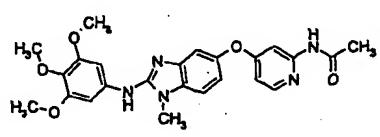
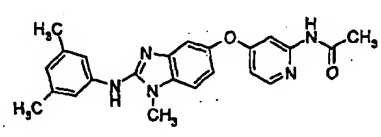
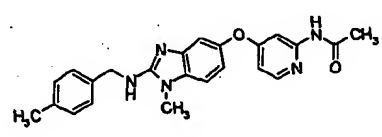
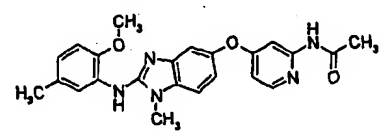
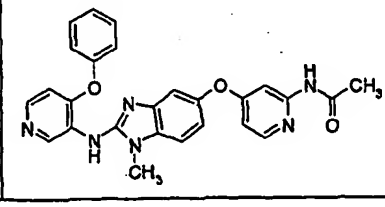
Ex.	Structure	Name	MH+
447		(3R)-N-[4-({2-[(2-fluoro-5-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpyrrolidine-3-carboxamide	531.2
448		(3R)-N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropylpyrrolidine-3-carboxamide	545.2
449		(3R)-N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}-1-isopropylpyrrolidine-3-carboxamide	557.1
450		N-[4-({2-[(3-tert-butylphenyl)-amino]quinolin-6-yl}oxy)pyridin-2-yl]acetamide	427.5
451		N-[4-({2-[(4-chloro-3-pyridin-4-ylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	485.9
452		N-{4-[(1-methyl-2-{[4-(4-methylpiperazin-1-yl)phenyl]-amino}-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	472.6
453		N-{4-({1-methyl-2-[(4-morpholin-4-ylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	459.5
454		N-{4-[(2-{[5-(2-chloropyridin-3-yl)-2-fluorophenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}acetamide	503.9

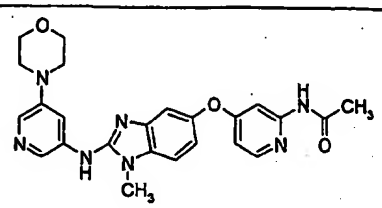
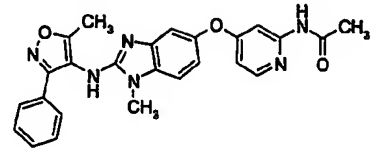
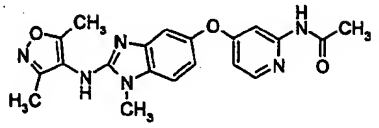
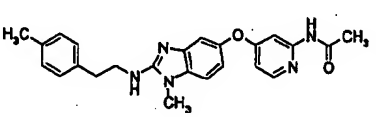
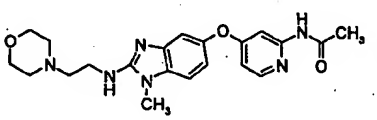
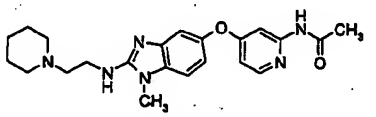
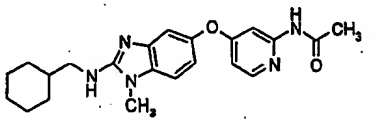
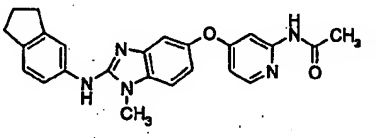
Ex.	Structure	Name	MH+
455		N-{4-[(2-{[4-chloro-3-(2-chloro-pyridin-3-yl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	520.4
456		N-[4-({2-[(3-isopropylphenyl)-amino]-1,3-benzoxazol-5-yl}-oxy)pyridin-2-yl]acetamide	403.5
457		N-[4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-methylpiperazine-1-carboxamide	514.6
458		N-[4-({2-[(3-tert-butyl-4-chloro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-methylpiperazine-1-carboxamide	549.1
459		N-[4-({2-[(4-chloro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-methylpiperazine-1-carboxamide	535.1
460		N-[4-({2-[(4-fluoro-3-isopropyl-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-4-methylpiperazine-1-carboxamide	518.6
461		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-4-methylpiperazine-1-carboxamide	544.5
462		N-[4-({2-[(3-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]pyrrolidine-3-carboxamide	485.6

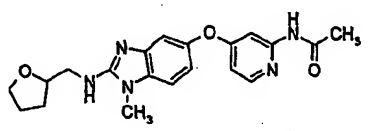
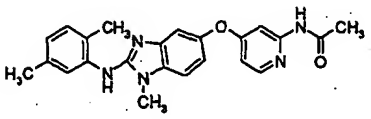
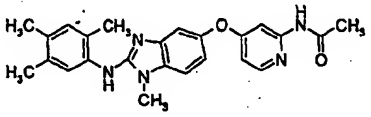
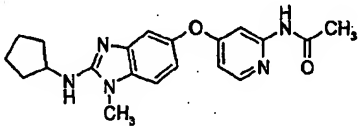
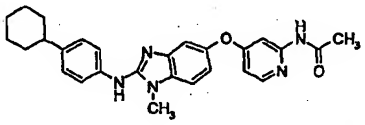
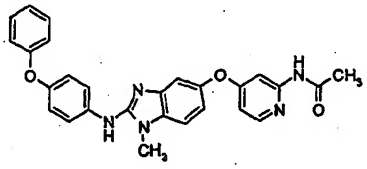
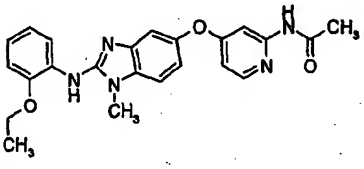
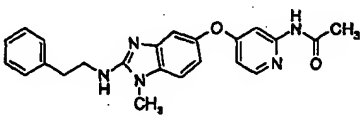
Ex.	Structure	Name	MH+
463		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropyl-piperidine-4-carboxamide	513.7
464		N-[4-({2-[(4-fluorophenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-1-isopropyl-piperidine-4-carboxamide	503.6
465		N-[4-({2-[(2,4-difluoro-5-isopropylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}-oxy)pyridin-2-yl]-2-(4-isopropyl-piperazin-1-yl)acetamide	578.7
466		N-[4-({2-[(3-tert-butylisoxazol-5-yl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	421.5
467		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-2-(1H-pyrrol-1-yl)-acetamide	525.5
468		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-1-(2-hydroxy-ethyl)piperidine-4-carboxamide	590.0
469		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-2-[(3R)-3-hydroxy-pyrrolidin-1-yl]acetamide	545.5
470		N-{4-[(2-{[2-chloro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-1-isopropyl-piperidine-4-carboxamide	588.0

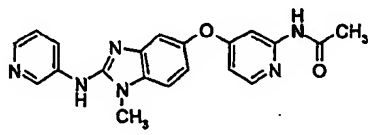
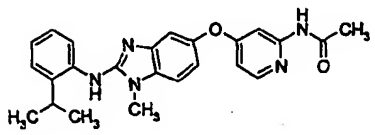
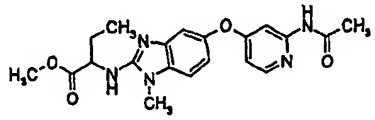
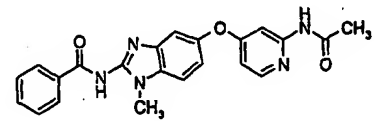
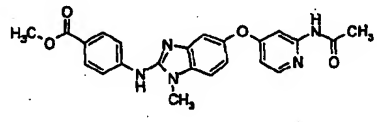
Ex.	Structure	Name	MH+
471		2-[(3R)-3-(dimethylamino)-pyrrolidin-1-yl]-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)-phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	572.6
472		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-2-[4-(trifluoro-methyl)-1H-imidazol-1-yl]-acetamide	594.5
473		N-[4-({2-[(5-tert-butyl-2-fluoro-phenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(4-methoxypiperidin-1-yl)-acetamide	561.7
474		N-[4-({2-[(3-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-methoxyazetidin-1-yl)acetamide	487.6
475		N-[4-({2-[(4-ethylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-methoxyazetidin-1-yl)acetamide	487.6
476		N-[4-({2-[(4-tert-butylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]-2-(3-methoxyazetidin-1-yl)-acetamide	515.6
477		1-ethyl-4-[2-({4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)-oxy]pyridin-2-yl}amino)-2-oxoethyl]-1-hydroxypiperazin-1-ium	589.6
478		N-{4-[(2-{[2-fluoro-5-(trifluoro-methyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}-2-piperazin-1-yl-acetamide	544.5

Ex.	Structure	Name	MH+
479		N-(4-{[2-(cyclohexylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	380.5
480		N-[4-({1-methyl-2-[(1-phenylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
481		N-(4-{[2-(mesitylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}pyridin-2-yl)acetamide	416.5
482		N-[4-({2-[(2,3-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
483		N-[4-({2-[(2-furylmethyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	378.4
484		N-[4-({2-[(3,4-dimethoxyphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	434.5
485		N-(4-{[2-(1,1'-biphenyl-2-yl-amino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	450.5
486		N-{4-[(2-{[2-(4-chlorophenyl)-ethyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	436.9

Ex.	Structure	Name	MH+
487		N-(4-{[2-(isobutylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}pyridin-2-yl)acetamide	354.4
488		N-(4-{[2-(isopropylamino)-1-methyl-1H-benzimidazol-5-yl]-oxy}pyridin-2-yl)acetamide	340.4
489		N-[4-({2-[(2-ethyl-6-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	416.5
490		N-[4-({1-methyl-2-[(3,4,5-trimethoxyphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	464.5
491		N-[4-({2-[(3,5-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
492		N-[4-({1-methyl-2-[(4-methylbenzyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
493		N-[4-({2-[(2-methoxy-5-methylphenyl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	418.5
494		N-[4-({1-methyl-2-[(4-phenoxypyridin-3-yl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	467.5

Ex.	Structure	Name	MH+
495		N-[4-({1-methyl-2-[(5-morpholin-4-ylpyridin-3-yl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	460.5
496		N-[4-({1-methyl-2-[(5-methyl-3-phenylisoxazol-4-yl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	455.5
497		N-[4-({2-[(3,5-dimethylisoxazol-4-yl)amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	393.4
498		N-{4-[(1-methyl-2-{[2-(4-methylphenyl)ethyl]amino}-1H-benzimidazol-5-yl)oxy]pyridin-2-yl}acetamide	416.5
499		N-[4-({1-methyl-2-[(2-morpholin-4-ylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	411.5
500		N-[4-({1-methyl-2-[(2-piperidin-1-ylethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	409.5
501		N-[4-({2-[(cyclohexylmethyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	394.5
502		N-(4-{[2-(2,3-dihydro-1H-inden-5-ylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	414.5

Ex.	Structure	Name	MH+
503		N-[4-({1-methyl-2-[(tetrahydro-furan-2-ylmethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	382.4
504		N-[4-({2-[(2,5-dimethylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5
505		N-[4-({1-methyl-2-[(2,4,5-trimethylphenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	416.5
506		N-(4-[[2-(cyclopentylamino)-1-methyl-1H-benzimidazol-5-yl]oxy}pyridin-2-yl)acetamide	366.4
507		N-[4-({2-[(4-cyclohexylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	456.6
508		N-[4-({1-methyl-2-[(4-phenoxy-phenyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	466.5
509		N-[4-({2-[(2-ethoxyphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	418.5
510		N-[4-({1-methyl-2-[(2-phenyl-ethyl)amino]-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	402.5

Ex.	Structure	Name	MH+
511		N-(4-{[1-methyl-2-(pyridin-3-yl-amino)-1H-benzimidazol-5-yl]-oxy}pyridin-2-yl)acetamide	375.4
512		N-[4-({2-[(2-isopropylphenyl)-amino]-1-methyl-1H-benzimidazol-5-yl}oxy)pyridin-2-yl]acetamide	416.5
513		methyl 2-[(5-{[2-(acetylamino)pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-yl)amino]butanoate	398.4
514		N-(5-{[2-(acetylamino)pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-yl)benzamide	402.4
515		methyl 4-[(5-{[2-(acetylamino)-pyridin-4-yl]oxy}-1-methyl-1H-benzimidazol-2-yl)amino]-benzoate	432.4

Example 516

Raf/Mek Filtration Assay

Buffers

Assay buffer: 50 mM Tris, pH 7.5, 15 mM $MgCl_2$, 0.1 mM EDTA, 1 mM DTT

Wash buffer: 25 mM Hepes, pH 7.4, 50 mM sodium pyrophosphate, 500 mM NaCl

Stop reagent: 30 mM EDTA

Materials

Raf, active:	Upstate Biotech #14-352
Mek, inactive:	Upstate Biotech #14-205
^{33}P-ATP:	NEN Perkin Elmer #NEG 602 h

96 well assay plates:	Falcon U-bottom polypropylene plates #35-1190
Filter apparatus:	Millipore #MAVM 096 OR
96 well filtration plates:	Millipore Immobilon 1 #MAIP NOB
Scintillation fluid:	Wallac OptiPhase "SuperMix" #1200-439

Assay conditions

Raf approximately 120 pM

Mek approximately 60 nM

^{33}P-ATP 100 nM

Reaction time 45-60 minutes at room temperature

Assay protocol

Raf and Mek were combined at 2X final concentrations in assay buffer (50 mM Tris, pH 7.5, 15 mM $MgCl_2$. 0.1 mM EDTA and 1 mM DTT) and dispensed 15 µl per well in polypropylene assay plates (Falcon U-bottom polypropylene 96 well assay plates #35-1190. Background levels are determined in wells containing Mek and DMSO without Raf.

To the Raf/Mek containing wells was added 3 µl of 10X of a raf kinase inhibitor test compound diluted in 100% DMSO. The raf kinase activity reaction was started by the addition of 12 µl per well of 2.5X ^{33}P-ATP diluted in assay buffer. After 45-60 minutes, the reactions were stopped with the addition of 70 µl of stop reagent (30 mM EDTA). Filtration plates were pre-wetted for 5 min with 70% ethanol, and then rinsed by filtration with wash buffer. Samples (90 µl) from the reaction wells were then transferred to the filtration plates. The filtration plates were washed 6X with wash buffer using Millipore filtration apparatus. The plates were dried and 100 µl per well of scintillation fluid (Wallac OptiPhase "SuperMix" #1200-439) was added. The CPM is then determined using a Wallac Microbeta 1450 reader.

Example 517

ASSAY 2: Biotinylated Raf Screen

In Vitro Raf Screen

The activity of various isoforms of Raf serine/threonine kinases (e.g., c-Raf, B-Raf and mutant B-Raf (V599E); see, for example, "Mechanism of Activation of the RAF-ERK Signaling Pathway by Oncogenic Mutations of B-RAF", *Cell* **116:** 855-867 (March 19, 2004); and "Dynamic Changes in C-Raf Phosphorylation and 14-3-3 Protein Binding

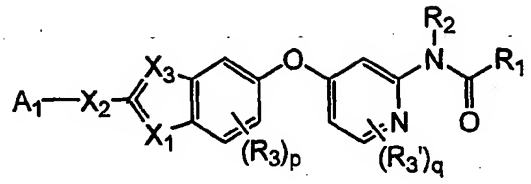
in Response to Growth Factor Stimulation - Differential Roles Of 14-3-3 Protein Binding Sites", *Journal of Biological Chemistry* **279(14):** 14074-14086 (April 2, 2004)) can be measured by providing ATP, MEK substrate, and assaying the transfer of phosphate moiety to the MEK residue. Recombinant isoforms of Raf were obtained by purification from sf9 insect cells infected with a human Raf recombinant baculovirus expression vector. Recombinant kinase inactive MEK was expressed in *E. coli* and labeled with Biotin post purification. For each assay, test compounds were serially diluted in DMSO then mixed with Raf (0.50 nM) and kinase inactive biotin-MEK (50 nM) in reaction buffer plus ATP (1 μM). Reactions were subsequently incubated for 2 hours at room temperature and stopped by the addition of 0.5 M EDTA. Stopped reaction mixture was transferred to a neutradavin-coated plate (Pierce) and incubated for 1 hour. Phosphorylated product was measured with the DELFIA time-resolved fluorescence system (Wallac), using a rabbit anti-p-MEK (Cell Signaling) as the primary antibody and europium labeled anti-rabbit as the secondary antibody. Time resolved fluorescence was read on a Wallac 1232 DELFIA fluorometer. The concentration of each compound for 50% inhibition (IC_{50}) was calculated by non-linear regression using XL Fit data analysis software.

Using the procedures of Example 517, the compounds of Examples 1-466, 468-476 and 478 were shown to have a raf kinase inhibitory activity at an IC_{50} of less than 10 μM.

While the preferred embodiments of the invention has been illustrated and described, it will be appreciated that various changes can be made therein without departing from the spirit and scope of the invention.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A compound of the formula (I):



(I)

wherein, X_1 and X_3 are independently selected from N, -NR_4-, -O- or –S-, wherein R_4 is hydrogen or loweralkyl, provided that at least one of X_1 and X_3 must be N or -NR_4-;

X_2 is –NH- or –$(CH_2)_m$- , wherein m is 0, 1, 2, 3 or 4;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryloweralkyl, heteroaryloweralkyl, alkyloxy-alkylheterocycloloweralkyl, or heteroaryloweralkyl;

R_2 is hydrogen or loweralkyl;

each R_3 and R_3' are independently selected from hydrogen, halogen, hydroxy, cyano, loweralkyl, or loweralkoxy; and

p and q are independently 0, 1, 2 or 3; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

2. A compound of Claim 1 wherein X_1 is -NR_4-.

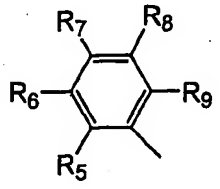
3. A compound of Claim 2 wherein R_4 is hydrogen.

4. A compound of Claim 2 wherein R_4 is methyl.

5. A compound of Claim 1 wherein X_2 is –NH-.

6. A compound of Claim 1 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkyl-phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, dihalophenyl, nitro-phenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkyl-fluorophenyl, trifluoromethylchlorophenyl, trifluoromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-fluoren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

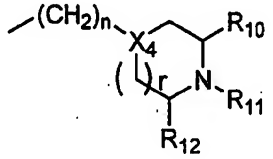
7. A compound of Claim 1 wherein A_1 has the structure:



wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

8. A compound of Claim 7 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

9. A compound of Claim 1 wherein R_1 has the structure:



wherein n is 0, 1, 2, 3 or 4;

r is 1 or 2;

X_4 is –CH- or N

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

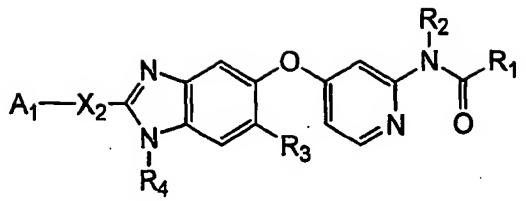
R_{11} is hydrogen, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

10. A compound of Claim 9 wherein n is 1.

11. A compound of Claim 9 wherein R_{10} and R_{12} are hydrogen or loweralkyl.

12. A compound of Claim 9 wherein R_{11} is loweralkyl.

13. A compound of the formula (II):



(II)

wherein, X_2 is –NH- or $-(CH_2)_m-$, wherein m is 0, 1, 2, 3 or 4;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryllowerallkyl, heteroaryllowerallkyl, alkyloxy-alkylheterocycloloweralkyl, or heteroaryllowerallkyl;

R_2 is hydrogen or loweralkyl;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy; and

R_4 is hydrogen or loweralkyl or

a pharmaceutically acceptable salt, ester or prodrug thereof.

14. A compound of Claim 13 wherein R_4 is hydrogen.

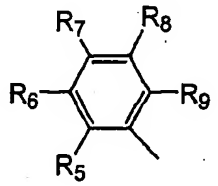
15. A compound of Claim 13 wherein R_4 is methyl.

16. A compound of Claim 13 wherein X_2 is –NH-.

17. A compound of Claim 13 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkyl-phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, dihalophenyl, nitro-phenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkyl-fluorophenyl, trifluoromethylchlorophenyl, trifluoromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, alkoxybiphenyl,

morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-fluoren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

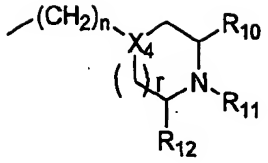
18. A compound of Claim 13 wherein A_1 has the structure:



wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

19. A compound of Claim 18 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

20. A compound of Claim 13 wherein R_1 has the structure:



wherein n is 0, 1, 2, 3 or 4;

r is 1 or 2;

X_4 is –CH- or N

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, halololoweralkyl, hydroxyloweralkyl, loweralkyloxy, halololoweralkyloxy, loweralkyl-sulfonyl, halololoweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

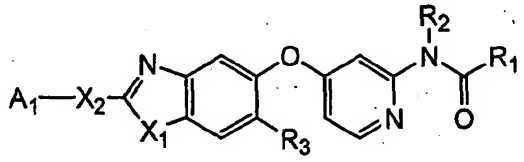
R_{11} is hydrogen, loweralkyl, halololoweralkyl, hydroxyloweralkyl, loweralkyloxy, halololoweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

21. A compound of Claim 20 wherein n is 1.

22. A compound of claim 20 wherein R_{10} and R_{12} are hydrogen or loweralkyl.

26. A compound of Claim 20 wherein R_{11} is loweralkyl.

27. A compound of the formula (III):



(III)

wherein, X_1 is -NR_4-, -O- or –S-, wherein R_4 is hydrogen or loweralkyl;

X_2 is –NH- or –$(CH_2)_m$- , wherein m is 0, 1, 2, 3 or 4;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl,

alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, arylloweralkyl, heteroarylloweralkyl, alkyloxy-alkylheterocyclooloweralkyl, or heteroarylloweralkyl;

R_2 is hydrogen or loweralkyl; and

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

28. A compound of Claim 27 wherein X_1 is -NR_4-.

29. A compound of Claim 28 wherein R_4 is hydrogen.

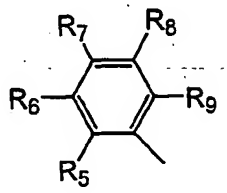
30. A compound of Claim 28 wherein R_4 is methyl.

31. A compound of Claim 27 wherein X_2 is –NH-.

32. A compound of Claim 27 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkyl-phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, dihalophenyl, nitro-phenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkyl-fluorophenyl, trifluoromethylchlorophenyl, trifluoromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-fluoren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl,

hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

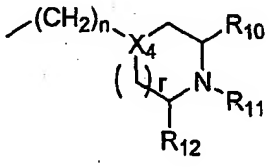
33. A compound of Claim 30 wherein A_1 has the structure:



wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

34. A compound of Claim 33 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

34. A compound of Claim 27 wherein R_1 has the structure:



wherein n is 0, 1, 2, 3 or 4;

r is 1 or 2;

X_4 is –CH- or N

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

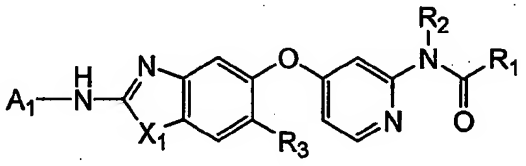
R_{11} is hydrogen, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

35. A compound of Claim 34 wherein n is 1.

36. A compound of Claim 34 wherein R_{10} and R_{12} are hydrogen or loweralkyl.

37. A compound of Claim 34 wherein R_{11} is loweralkyl.

38. A compound of the formula (IV):



(IV)

wherein X_1 is -NR_4-, -O- or –S-, wherein R_4 is hydrogen or loweralkyl;

A_1 is substituted or unsubstituted alkyl, cycloalkyl, heterocycloalkyl, aryl, polycyclic aryl, polycyclic arylalkyl, heteroaryl, biaryl, heteroarylaryl, or heteroarylheteroaryl;

R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryloweralkyl, heteroaryloweralkyl, alkyloxy-alkylheterocycloloweralkyl, or heteroaryloweralkyl;

R_2 is hydrogen or loweralkyl; and

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy; or

a pharmaceutically acceptable salt, ester or prodrug thereof.

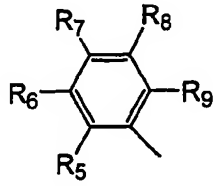
39. A compound of Claim 38 wherein X_1 is -NR_4-.

40. A compound of Claim 39 wherein R_4 is hydrogen.

41. A compound of Claim 39 wherein R_4 is methyl.

42. A compound of Claim 38 wherein A_1 is selected from the group consisting of substituted or unsubstituted phenyl, pyridyl, pyrimidinyl, phenylalkyl, pyridylalkyl, pyrimidinylalkyl, heterocyclylcarbonylphenyl, heterocyclylphenyl, heterocyclylalkyl-phenyl, chlorophenyl, fluorophenyl, bromophenyl, iodophenyl, dihalophenyl, nitro-phenyl, 4-bromophenyl, 4-chlorophenyl, alkylbenzoate, alkoxyphenyl, dialkoxyphenyl, dialkylphenyl, trialkylphenyl, thiophene, thiophene-2-carboxylate, alkylthiophenyl, trifluoromethylphenyl, acetylphenyl, sulfamoylphenyl, biphenyl, cyclohexylphenyl, phenyloxyphenyl, dialkylaminophenyl, alkylbromophenyl, alkylchlorophenyl, alkyl-fluorophenyl, trifluoromethylchlorophenyl, trifluoromethylbromophenyl indenyl, 2,3-dihydroindenyl, tetralinyl, trifluorophenyl, (trifluoromethyl)thiophenyl, alkoxybiphenyl, morpholinyl, N-piperazinyl, N-morpholinylalkyl, piperazinylalkyl, cyclohexylalkyl, indolyl, 2,3-dihydroindolyl, 1-aceyt1-2,3-dihydroindolyl, cycloheptyl, bicyclo[2.2.1]hept-2-yl, hydroxyphenyl, hydroxyalkylphenyl, pyrrolidinyl, pyrrolidin-1-yl, pyrrolidin-1-ylalkyl, 4-amino(imino)methylphenyl, isoxazolyl, indazolyl, adamantyl, bicyclohexyl, quinuclidinyl, imidazolyl, benzimidazolyl, imidazolylphenyl, phenylimidazolyl, pthalamido, napthyl, benzophenone, anilinyl, anisolyl, quinolinyl, quinolinonyl, phenylsulfonyl, phenylalkylsulfonyl, 9H-fluoren-1-yl, piperidin-1-yl, piperidin-1-ylalkyl, cyclopropyl, cyclopropylalkyl, pyrimidin-5-ylphenyl, quinolidinylphenyl, furanyl, furanylphenyl, N-methylpiperidin-4-yl, pyrrolidin-4-ylpyridinyl, 4-diazepan-1-yl, hydroxypyrrolidn-1-yl, dialkylaminopyrrolidin-1-yl, 1,4'-bipiperidin-1'-yl, and (1,4'-bipiperidin-1'-ylcarbonyl)phenyl.

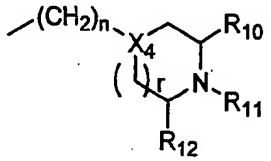
43. A compound of Claim 38 wherein A_1 has the structure:



wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

44. A compound of Claim 38 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

45. A compound of Claim 38 wherein R_1 has the structure:



wherein n is 0, 1, 2, 3 or 4;

r is 1 or 2;

X_4 is –CH- or N

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

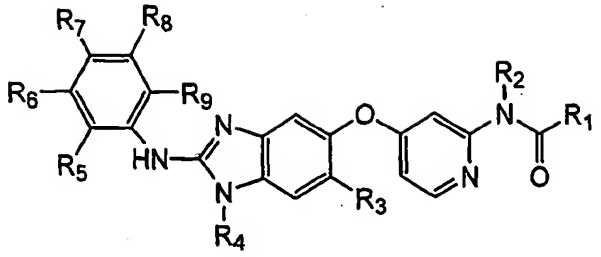
R_{11} is hydrogen, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

46. A compound of Claim 45 wherein n is 1.

47. A compound of Claim 45 wherein R_{10} and R_{12} are hydrogen or loweralkyl.

48. A compound of Claim 45 wherein R_{11} is loweralkyl.

49. A compound of the formula (V):



(V)

wherein R_1 is hydrogen or substituted or unsubstituted loweralkyl, alkoxyalkyl, loweralkyloxy, amino, aminoalkyl, cycloalkyl, heterocycloalkyl, aryl, heteroaryl, alkyloxyalkylheterocycloalkyl, heteroarylalkyl, cycloalkyloweralkyl, heterocycloalkyl-loweralkyl, loweralkylheterocycloalkyl, aryloweralkyl, heteroaryloweralkyl, alkyloxy-alkylheterocycloloweralkyl, or heteroaryloweralkyl;

R_2 is hydrogen or loweralkyl;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl; and

R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkylthio, haloloweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; or

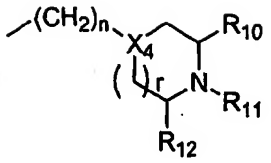
a pharmaceutically acceptable salt, ester or prodrug thereof.

50. A compound of Claim 49 wherein R_4 is hydrogen.

51. A compound of Claim 49 wherein R_4 is methyl.

52. A compound of Claim 49 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

53. A compound of Claim 49 wherein R_1 has the structure:



wherein n is 0, 1, 2, 3 or 4;

r is 1 or 2;

X_4 is –CH- or N

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyl-sulfonyl, haloloweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

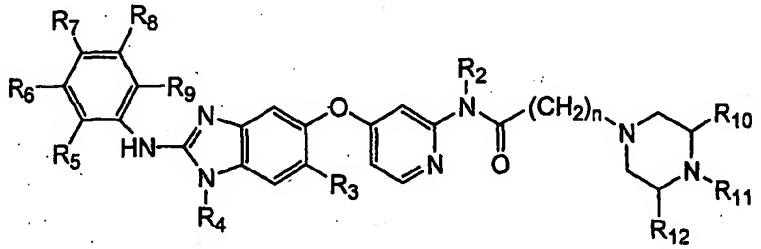
R_{11} is hydrogen, loweralkyl, haloloweralkyl, hydroxyloweralkyl, loweralkyloxy, haloloweralkyloxy, loweralkyloxyloweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl.

54. A compound of Claim 53 wherein n is 1.

55. A compound of Claim 53 wherein R_{10} and R_{12} are hydrogen or loweralkyl.

56. A compound of Claim 53 wherein R_{11} is loweralkyl.

57. A compound of the formula (VI):



(VI)

R_2 is hydrogen or loweralkyl;

R_3 is hydrogen, halogen, loweralkyl, or loweralkoxy;

R_4 is hydrogen or loweralkyl; and

R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, halo, loweralkyl, cyano, hydroxy, haloloweralkyl, loweralkyloxy, haloloweralkyloxy,

loweralkylthio, halologweralkylthio, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl;

n is 0, 1, 2, 3 or 4;

R_{10} and R_{12} are independently selected from hydrogen, halo, loweralkyl, halologweralkyl, hydroxylogweralkyl, loweralkyloxy, halologweralkyloxy, loweralkyl-sulfonyl, halologweralkylsulfonyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl; and

R_{11} is hydrogen, loweralkyl, halologweralkyl, hydroxylogweralkyl, loweralkyloxy, halologweralkyloxy, loweralkyloxylogweralkyl, and substituted or unsubstituted cycloalkyl, heterocycloalkyl, aryl, or heteroaryl or

a pharmaceutically acceptable salt, ester or prodrug thereof.

58. A compound of Claim 57 wherein A compound of Claim 49 wherein R_4 is hydrogen.

59. A compound of Claim 57 wherein R_4 is methyl.

60. A compound of Claim 57 wherein R_5, R_6, R_7, R_8 and R_9 are independently selected from hydrogen, chloro, fluoro, methyl, ethyl, propyl, *iso*-propyl, butyl, *tert*-butyl, cyano, hydroxy, methyloxy, trifluoromethyl, trifluoromethoxy, trifluoromethylthio, acetyl, and substituted or unsubstituted phenyl, phenyloxy, furyl, tetrahydrofuranyl, tetrahydropyranyl, pyridinyl, trifluoromethylpiperidinyl, thiophenyl, piperazinyl, and morpholinyl.

61. A compound of Claim 57 wherein wherein n is 1.

62. A compound of Claim 57 wherein wherein R_{10} and R_{12} are hydrogen or loweralkyl.

63. The compound of Claim 57 which is 2-(4-ethylpiperazin-1-yl)-N-{4-[(2-{[2-fluoro-5-(trifluoromethyl)phenyl]amino}-1-methyl-1H-benzimidazol-5-yl)oxy]-pyridin-2-yl}acetamide.

64. A composition comprising an amount of a compound of claims 1, 13, 27, 38, 49, 57 or 63 effective to inhibit Raf activity in a human or animal subject when administered thereto, together with a pharmaceutically acceptable carrier.

65. A composition of Claim 64 which further comprises at least one additional agent for the treatment of cancer.

66. A composition of Claim 65 in which the at least one additional agent for the treatment of cancer is selected from dacarbazine, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

67. A method of inhibiting Raf kinase activity in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 13, 27, 38, 49, 57 or 63 effective to inhibit Raf kinase activity in the human or animal subject.

68. A method for treating a cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 13, 27, 38, 49, 57 or 63 effective to inhibit Raf kinase activity in the human or animal subject.

69. A method of Claim 68 wherein said cancer is melanoma, papillary thyroid cancer, cholangiocarcinoma, gallbladder carcinoma, colorectal cancer, lung cancer, pancreatic cancer, leukemia, prostate cancer, ovarian cancer, breast cancer, or lung cancer.

70. A method of claim 68 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

71. A method of claim 70 in which the at least one additional agent for the treatment of cancer is selected from dacarbazine, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

72. A method for treating a hormone dependent cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 13, 27, 38, 49, 57 or 63 effective to inhibit Raf kinase activity in the human or animal subject.

73. A method of claim 72 wherein the hormone dependent cancer is breast cancer or prostate cancer.

74. A method of claim 72 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

75. A method of claim 74 in which the at least one additional agent for the treatment of cancer is selected from dacarbazine, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

76. A method for treating a hematological cancer disorder in a human or animal subject, comprising administering to the human or animal subject a composition comprising an amount of a compound of claims 1, 13, 27, 38, 49, 57 or 63 effective to inhibit Raf kinase activity in the human or animal subject.

77. A method of claim 76 which further comprises administering to the human or animal subject at least one additional agent for the treatment of cancer.

78. A method of claim 77 in which the at least one additional agent for the treatment of cancer is selected from dacarbazine, irinotecan, topotecan, gemcitabine, 5-fluorouracil, leucovorin carboplatin, cisplatin, taxanes, tezacitabine, cyclophosphamide, vinca alkaloids, imatinib, anthracyclines, rituximab and trastuzumab.

79. A compound of claims 1, 13, 27, 38, 49, 57 or 63 for use as a pharmaceutical.

80. Use of a compound of claims 1, 13, 27, 38, 49, 57 or 63 in the manufacture of a medicament for the treatment of cancer.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US2004/034179

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/4184 A61K31/428 C07D401/12 C07D405/14 C07D401/14
C07D417/12 C07D409/14 C07D413/14 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/082272 A1 (CHIRON CORPORATION; RENHOWE, PAUL, A; RAMURTHY, SAVITHRI; AMIRI, PAYMA) 9 October 2003 (2003-10-09) claims 1,74	1-80
A	WO 02/094808 A1 (SMITHKLINE BEECHAM P.L.C; DEAN, DAVID, KENNETH; TAKLE, ANDREW, KENNETH) 28 November 2002 (2002-11-28) claim 1 page 1, lines 3-24	1-80

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 January 2005	04/02/2005

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Bérillon, L

Form PCT/ISA/210 (second sheet) (January 2004)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/034179

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 67-78
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 67-78 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US2004/034179

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03082272 A1	09-10-2003	US 2004087626 A1	06-05-2004
		US 2004122237 A1	24-06-2004
WO 02094808 A1	28-11-2002	EP 1397354 A1	17-03-2004
		JP 2004529967 T	30-09-2004
		US 2004127496 A1	01-07-2004